# STUDIES IN EPIDEMIOLOGY

With special reference to plague and including an account of a recent epidemic, at Santipur, Nadia, Bengal.

A

Thesis for the degree of

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of the

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by

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# Introduction.

In the few lines with which I am about to preface this work, it is my desire first of all to make clear the reasons that have influenced and the circumstances that have led me to take up, as a very special study, the subjects comprised under the heading of Public Health or Sanitary Science, and to prosecute such study to the furthest limits possible. Quite well do I remember the day, now more than a decade of years ago, when Alma Mater deemed me sufficiently worthy to receive the first honours at her hands and conferred on me the right, title and privilege to practise my profession on my fellow beings. I also remember well the feelings of proud satisfaction with which I received those gifts, perhaps scarcely realising at the time that my days for study had really only just commenced, that I was the veriest novice at the work I would henceforth have to perform, and that I had not acquired so much knowledge in professional work that I was never likely to require more. Very soon, however, I launched into the world of practical medicine and was not long in discovering that any feeling of confidence I had within me was by no means unmixed with something of diffidence. Thus, for the next three years, while, on the one hand, I strove to discharge my duties conscientiously, I set myself, on the other, to find out what the requirements in each department of practice were, and, by testing my own powers, to gain a definite knowledge of my capabilities in each branch in relation to its needs. This consideration very soon resulted in engendering within me a feeling of discontent, accompanied with a spirit of ambition. I felt, especially with regard to the subjects included in the study of public health, that my knowledge at the time was only of a very average standard and not equal to the requirements which, in that particular branch, were extending day by day. I say I felt discontented at this and it naturally became my ambition to equalise supply and demand by improving myself to the required standard. At the same time I well knew that Medicine and Surgery too had been making progress with giant strides and, resolving to take the same opportunity to bring myself abreast of these advances, I made haste to return to my University in 1899. I discovered that during my short stay abroad an enormous amount of new work had been done in many directions but most particularly in two, namely in bacteriology and in medicine in relation to public health. A wider experience and an accumulation of facts recently brought to light, had made it necessary for workers on these subjects to scrutinise again old observations and to readjust ideas that had held sway for no short period of time. To the study of such then was it my pleasant duty to apply myself and my good fortune to be able to devote my energies, for the necessity for a high standard of proficiency in these directions was particularly pressing in India where my lot was cast to practise my calling, where ideas regarding sanitation were still in their earliest infancy, where plague and pestilence raged rampant and where one constantly found that whether in a professional or in an official capacity, one was responsible both to God and to man for the health and well-being of a number of people which, though a mere fraction of the 300 millions that populate the country, still amounted to a few hundred thousand souls. It is not easy for one who does not know of the multifarious duties that fall to the medical man in State service in these parts to realise how in a moment he may be called upon to turn his attention from ordinary medico-surgical work to problems in hygiene involving the welfare of large communities of beings. Thus, I can readily recall to memory some of the numerous questions on which my opinion has, from time to time, been sought, e.g. problems concerning large drainage schemes, questions regarding the seasonal influence on birth- and death-rates in Bengal, the types of fever prevalent in particular districts in the province, and their causes, questions on vaccination, on the occurrence of epizootics, and a host of other subjects, for the information of administrative officers, heads of departments, for the revision of gazeteers or for dealing with epidemic outbreaks or undertaking large sanitary reforms. With a view to acquiring a fuller knowledge on these and similar matters, did I devote myself particularly to the special study of public health, while, at the same time, I did not fail to improve myself in the other departments of medicine as well as in science generally, with results that were very gratifying to me indeed but to recount which would savour too much of egotism. In 1901, having been specially selected by the Government for X-ray work, to the scientific aspect of which I had devoted myself very thoroughly, I was sent out to India where another period of active work awaited me. How often since have I not had occasion to thank my good fortune for the excellent teachings of my masters and the special training I had received in the department of public health. I recollect well such occasions for instance as when some two years ago I was, of a sudden, called upon from the midst of ordinary hospital work to act as Medical Officer of Health for an important trans-Indus cantonment on the north-west frontier of India, which was threatened with an invasion of plague from the adjoining city. The good stead in which the precepts I had acquired, stood me, during my term of office, was evidenced by the clean bill of health I was able to preserve throughout the time, an occasion of some responsibility and not without its anxieties. Three years of work abroad soon passed again and left me, as I began to feel, once more behind the times, and so the desire seized me afresh to revisit the Temple of Learning and gain more knowledge of my work as well as more honours from Alma Mater whose bounties had already been so great that never would it be possible for me to discharge the debt of gratitude I owed her. The year 1905 saw me back again at Modern Athens to still further carry on the studies that had already proved so beneficial to me. The Fellowship of the Royal College of Surgeons, which I had long coveted,I obtained. With the greatest interest and much advantage I followed the excellent and up to date course of instruction at the University on the Diseases of Tropical Climates. Then, last but not least, through the great kindness of the Professor of Public Health and of the Dean of the Faculty of Science, I was permitted to appear at a"special" for the Doctorate of Science in Public Health, the degree that it became the summit of my ambition to obtain. The subject that was appointed for me to appear in, comprised a full study of the "Causes and methods of prevention of endemic and epidemic diseases as well as of epizootics, and of the contagious and infectious diseases with special reference to those diseases occurring in India". The wideness of scope of this subject, or rather set of subjects, taken into account with the high standard of knowledge required at the test, implied very extensive and advanced study. The magnitude of the task was a stimulus to my efforts, as the prize to be gained, in the shape of the highest degree in Public Health, was an incentive to my ambition. The happy nature of the result of both work done and ordeal passed through, I need only hint at by saying that, turning out as it did, it requires me this day to engage in the pleasant duty of writing these few lines. The extensive knowledge gained from the work on a most important group of subjects, was a big reward in itself and such that the benefits from it will not cease to be felt as long as life and health permit of my being engaged in active duties. To gain such a knowledge as this, which now it will be my constant endeavour to keep up and improve, on a subject I long since came to regard as one of the first importance to the efficient and honest discharge of my duties, was the reason that impelled me at first to take up as a special work the study of the subjects of Public Health, and subsequently to follow this up to the highest standard possible. And what is left now for me to say in these introductory lines? It yet remains that I should offer some explanation as to what directs me in the choice of subject for this thesis. As the matter appointed for the written examination had everything to do with epidemiology, my mind now naturally runs on this very excellent theme and suggests to me the making of this work in some sense, as it were, a sequel to a portion of what has gone before, for manifestly it is beyond the bounds of possibility to deal with epidemiology in its entirety, in a single short work such as the present. So much for this, but now, on attempting to proceed further, I am at once confronted with the difficulty of offering a suitable explanation or making an apology for such seeming presumption on my part as in daring to lift my pen for the purpose of writing, to any extent at all, on a subject which so great an authority as Sir Thomas Fraser, of Edinburgh, has recently dealt with in so masterly a manner in his Report, as President of the late Indian Plague Commission appointed in accordance with a Government of India Resolution dated November, 1898. But I may be allowed to say in exoneration of myself from blame for anything like presumption that, while my mind runs on the subject of epidemiology, it also dwells (to keep up the idea of the sequel) on that of the "contagious and infectious diseases with special reference to those diseases occurring in India". Owing partly to this and partly to the fact that my experience is largely Indian, I naturally tend to make special reference to a disorder, plague, the epidemiological bearings of which have a particular interest at the present time. For plague, so far as its recent pandemic occurrence is concerned, although of more than ten years duration in India, still continues to occupy a place of primary importance, not so much by reason of the numbers it kills,- for the "fevers" and cholera are more active in this respect,- as for the suddenness of its appearance, the extent of its range, the rapidity of its diffusion and its want of amenability to treatment. But there is yet another reason for my choice of subject leading me to refer particularly to this disease and it is that a small but what might be called, a smart epidemic of the dread disease broke out recently in a town within the "ilaka" or jurisdiction of the district of Nadia, shortly before my arrival, and in the management and suppression of which I had a good deal to do. The outbreak was illustrative of many features now thoroughly well recognised in the epidemiology of the disease and it was full of interest from the point of view of sanitarian and epidemiologist alike. A brief account of the outbreak will be included in this work and it will, I trust, prove of some interest. The way in which it was kept under control and prevented from extending over a large area, which it had many facilities for doing, in fact the manner in which it was hemmed in, within the municipal limits of the town where it started, show what energetic measures can do, if adopted on a sound and scientific basis and promptly carried out in practice.

Such then are the reasons that have influenced me to go far into the study of public health specially, and have, in the present instance, guided me in the selection of my subject. I trust I have rendered a sufficient explanation for my seeming boldness in launching out on so formidable a discussion. I venture to lay before my superiors my earnest endeavours at scientific work, and I trust that, having regard to the magnitude and difficulties of the task I have undertaken, they will look upon my efforts with not too critical an eye, remembering that a mere disciple writes what a master will read.

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# CHAPTER I.

## ON THE RELATION OF BACTERIOLOGY TO EPIDEMIOLOGY.

Before entering on the bacteriology and the epidemiology of plague, which subjects are to supply the material for a subsequent part of this work, it is proposed to commence by discussing briefly the relation which, in general, bacteriology bears to epidemiology. For, while each of these subjects is intensely interesting in itself to the seeker after scientific medical lore, it comes to be a matter of unrivalled interest and one that has a peculiarly seductive charm for the advanced reader and thinker, to consider the relationship in which these two branches of knowledge stand to one another. Moreover, such a study comprises a host of advances that have recently been made in most important directions, and in itself allows scope for the production of a very comprehensive thesis, but our endeavour will be to condense _multum in parvo_ and put as many facts as possible into the limited space of a single chapter of this small work. For, numerous indeed are the truths which have of late years been brought to light and one might venture to say that in no department of medical science has the student been confronted with such a multitude of facts freshly discovered within so comparatively short a period of time, as in that of bacteriology. And it is these discoveries which the bacteriologist has made that mark a new epoch in the history of the work of the epidemiologist and allow of his considering the causes of spread and the methods of prevention of the diseases with which he is concerned, in a rational manner and from a scientific standpoint. Now what was the conception which our forefathers of not so many centuries ago, had of disease generally ? To them all morbid conditions and processes meant the outcome of the malevolence of evil spirits, or were due to the agency of the Evil One, or were caused by witchcraft or by the visitations of God, or were produced by the caprice of the "stars in their courses" or other mysterious phenomena of Nature. Such were the ideas that prevailed down to the end of the seventeenth century, and the first step that was taken to advance them in a rational direction was by Athanasius Kircher when, in 1671, he drew attention to the agency of invisible organisms in the causation of disease, in his work entitled "Pathologia Animata". Four years later, in 1675, Leewenhoek did much work in the same direction, with his microscope. It was not very long afterwards that the theory of the "contagium vivum" emanated as the result of the studies of Plenciz, of Vienna, who was the first to enunciate the specific character of the "fons et origo mali" and to urge that each disease was a distinct identity produced by a separate cause which was transmissible through air, capable of falling on a suitable medium, of breeding there and, under suitable circumstances, ultimately giving rise to the manifestations peculiar to its presence and growth. In the wake of this advance followed a great discussion on "abiogenesis" or the spontaneous generation of disease, a theory which once found many adherents and was the subject of a prolonged controversy. The next great landmark in this history corresponds with the researches of such men as Lister, Pasteur and Koch, the result of which was to give an impetus to the theory and practice of hygiene with effects that reached far and wide throughout all the civilised world and more especially Great Britain, France and Germany. The ideas once formulated by men like these, were soon put into effect by the Sanitary Engineer, and lo! plague disappeared from our shores as by the wave of a magician's wand, while other filth-diseases, such as typhus, made as rapid and desirable an exit, and malaria vanished like dew before the rising sun! Pasteur at this time carried on his valuable researches on the subject of fermentations, and he was very soon able to confirm and elaborate the work of Naegeli and Latour on similar lines.

It was the same Pasteur who first converted into fact what the Viennese savant had put forward as only a theory, regarding the specific nature of disease, by showing that different organisms manifested different kinds of activity, for while some produced mere fermentative changes, others gave rise to definite and more or less serious disease, and still others were instrumental in the production of putrefaction. The next event in the process of evolution of knowledge on these matters was an emanation of the principles of antiseptic surgery as the outcome of Lister's researches into the causes of suppuration. It was only as recently as 1849, that the first organism found in a disease transmissible to man, was described, for in that year, Pollender furnished an account of the specific germ of anthrax, although it was not until fourteen years later, in 1863, that Davaine established the connection between organism and disease, a connection which has long since been amply and conclusively confirmed by Koch. What a debt of gratitude the world of medicine and of suffering humanity owe to the work of such eminent leaders as Lister, Pasteur and Koch, in that as the result of their labours, we are now familiar with a great number of disease-producing germs, some already proved beyond the shadow of a doubt to be pathogenic, others not yet fully demonstrated to be so, as some link in the chain of evidence is still missing although its place may be supplied by analogy, while still others continue to remain enveloped in mystery for the present. Manson puts it thus, "Modern science has clearly shown that nearly all diseases, directly or indirectly, are caused by germs. It must be confessed that although in many instances these germs have been discovered, in other instances they are yet to find; nevertheless, their existence in the latter may be confidently postulated". What then are the conditions that a given organism must fulfil in order to be regarded as the <u>sine qua non</u> of a disease? These were laid down very definitely by the great Robert Koch years ago and they are embodied in his classical"postulates" which are to the following effect,- (1) the pathogenic organism said to be the specific cause of a disease, must constantly be found in the tissues of an animal dead or suffering from the disease in question; (2) the organism taken from such a case must be cultivated outside the body, in artificial media, for any required number of successive generations; (3) the last of these obtained by this method, in pure culture i.e. purified of all extraneous matter, should be capable of setting up, in a healthy susceptible animal, the same disease process; (4) the organism must be discovered similarly distributed in the diseased tissues of this animal and must be recovered from such tissues,- this cycle of events must remain constant under similar conditions. This list of requirements Martin has supplemented with a fifth point or addendum, viz.

that the secondary infective agents, toxins or toxic products, occurring in pure artificial cultures of the organism, must be similar in chemical properties and in physiological actions to those separable from the tissues of animals that have acquired the disease in the ordinary way. So when an organism is found that satisfies all these conditions in relation to a particular disease, it is said to be the undoubted specific cause, for it will produce that disease and that disease alone, as is the case for instance with the anthrax, tuberculosis and tetanus organisms, without which their respective diseases cannot occur. It must, however, be remembered that all organisms are not so definite in their specific character, for, on the one hand, certain conditions, such as suppurative lesions, are caused by a variety of organisms, namely, the staphylococcus pyogenes aurues, albus and citreus, streptococcus pyogenes, bacillus pyocyaneus, pneumococcus, bacillus typhosus and the gonococcus; while, on the other hand, some organisms, like the pneumococcus (or diplococcus pneumoniae) discovered by Fraenkel, in 1884, are responsible for a variety of lesions differing clinically from one another, such as typical lobar pneumonia, empyema, acute osteomyelitis, purulent peritonitis and acute cerebro-spinal meningitis. The last is not to be mistaken for the epidemic disease known as cerebro-spinal fever of which a smart outbreak occurred in Austria from April to July, 1905, and which is due to the diplococcus intracellularis meningitidis, also called the tetracoccus intracellularis, of Weichselbaum, 1887,- a disease studied so carefully and written on so ably by Dr Bruce Low. Further, there are cases in which two or more organisms can act together in setting up the lesions of disease without, however, being absolutely dependent on each other or conforming to what is known in biology as "symbiosis". In cases of this kind the associated organisms so far act in conjunction that one lowers the vitality or powers of resistance of the tissues of the host, while the other gains a foothold, as for example when the staphylococcus pyogenes aureus acts in conjunction with the tetanus bacillus of Nicolaier.

Now let us concentrate our ideas on the special subject we have on hand, that is, the manner in which this host of bacteriological facts stands related to the question of epidemiology, but ere we attempt to do this let us form a clear notion of what exactly is meant by the term "epidemiology". This may be defined as the science which treats of the spread of disease, principally such diseases as have a tendency to spread over a large area or community, regardless of local circumstances (epidemic diseases), but not excluding those troubles which are generally confined to the inhabitants of a particular locality and are apparently influenced to a large extent by local conditions (endemic diseases). The ancients regarded the study of such maladies as a special study. On enquiry into the works of Oribasius, it is found that he regarded epidemic diseases as those which attack many persons together and have a common origin and a common cause. Hippocrates, who lived a little more than four centuries before Christ, makes many interesting remarks in his "Book of Epidemics", on the origin and nature of such diseases, attributing them especially to the quality of the air breathed. Claudius Galen, in his "Commentary on the Epidemics of Hippocrates", attributes the origin of epidemics, in a great measure, to the state of the atmosphere, but also holds that the nature of the country may contribute, and that a peculiar disposition of the body to admit such diseases is also necessary. Epidemics are also described and attributed to various causes of a similar kind by the old Arabian physicians, Avenzoar (Epid. iii), Haly Abbas (Theor,v,ii), Avicenna (IV,1,iv) and a large number of others. Returning from the ancient history on the subject to our present-day definition of epidemiology, we endeavour to shape our ideas on this very interesting and not altogether uncomplicated subject by taking into consideration and classifying, for the purposes of our study, the diseases that are comprised in it. To suit this object best, we divide the diseases which concern us at present, into two great groups and an intermediate set, the basis of such classification being the clinical and epidemiological features characteristic of them.

Group I.- The acute exanthemata,- including small-pox, scarlet fever, typhus, chicken pox, rubella, measles, and in some measure also whooping cough as well as mumps.

Group II.- Diseases with well marked local lesion from which as centre, the trouble radiates, including cholera, enteric fever, diphtheria, erysipelas, suppurative conditions with pyaemia and septicaemia, tetanus, tubercle, pneumonia, gonorrhoea, anthrax, rabies.

The following table contrasts the characteristic features belonging respectively to these groups of diseases,-

| | Group I. | Group II. |
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| (1)Clinical features. | General or systemic diseases with little or no tendency to local action. (The sore-throat of scarlet fever, the coryza of measles and the parotitis of mumps may be instanced against this, but these are more of the nature of concomitants of the diseases than evidence of initial or central lesion). | A well marked local lesion from which, as stated before, the disease as it were radiates. |

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| (2)Invasion | Acute, with well marked febrile disturbance. | Frequently less acute. |
| (3)Eruption | Well marked and characteristic. | As a rule inconspicuous, or may be absent. |
| (4)Infectiousness. | Of high degree. | Of low degree or absent. |
| (5)Epidemiological type | Almost exclusively epidemic in form | Generally endemic in form though under certain circumstances, tending to become epidemic. |
| (6)Immunity conferred by one attack. | For a considerable period and, in many cases, permanent. | Generally not so lasting and, in some cases, quite transient. |

Group III.- This consists of an intermediate set including influenza and plague, the former a disease of low immunising power but highly infectious, the latter a trouble with well defined local lesions, extending to the system in general, or, it may be, a general disease but concentrating in a typical manner in certain parts and capable of conferring immunity in a small measure.

With regard to the division of the main body of infective diseases into the first two groups, it has been stated that the classification was made on a basis of clinical and epidemiological differences. But this is not all, for there are bacteriological relations which lend support to the plan since bacteriological methods have hitherto entirely failed to discover the causae causantes of the various diseases of the first set in spite of the fact that, owing to the wideness of their prevalence and to their highly infectious character, these diseases have constantly attracted the attention of the keenest observers. In many instances claims for organisms of one kind and another have been advanced in connection with some of the diseases, yet, from a scientific point of view, we are bound at present to regard their specific nature as "non-proven". Such is the case, for instance, with the streptococcus said to have been discovered by Klein in the blood and tissues of persons suffering from scarlet fever and accredited with the causation of that disease; or the small bacillus found by Klein and Copeman in the early (fifth day) lymph of small-pox and vaccinia pustules and given the credit of being the cause of those conditions. Such is also the case with the extremely small "Guarnieri bodies" studied by Siegel, regarded by him as true parasites to be classed as a new group of sporozoa, specific of the lesions of variola and vaccinia, and, according to that observer, very similar to an organism found by him in the lesions of "foot and mouth" disease (known also by the numerous aliases of epidemic stomatitis, aphthous fever, murrain, aphtha and eczema epizootica). But whether proven or not, there can be little doubt that the causative agents at work in the affections of this group must be of the nature of parasitic organisms. Moreover, these diseases are highly infectious and the infective material seems to be air-borne, though the extent of the aerial transmissibility is not certain and is possibly very limited. Doubtless the infection may be carried by means of an intermediary in the form of a person or of fomites, for considerable distances. An important point mentioned in the table, in connection with the diseases of the first group, is their remarkable epidemic character. These troubles are propagated from case to case and do not arise "de novo" after the manner which Dr Milroy, apparently a believer in the doctrine of the "generatio de novo" of diseases, would have us believe. Similarly there is the recent work on "Heterogenesis" by Bastian who adduces facts and arguments to prove that simple forms of life, e.g., bacteria may either be built up from more simple substances, or even be the outcome of higher organisms. It is, however, now generally believed that such troubles, as we have been referring to, are propagated from person to person and, this being the case, the infective matter may retain its vitality and its power of giving rise to disease, outside the body, for a considerable time, but it has not the power of undergoing ectanthropic or, what Pettenkofer calls "ectogenous" multiplication. The point regarding the manner in which many of the pathogenic organisms behave extra-corporeally, has been a very much debated question. On the one hand, it has been argued that the infective material may lose its virulence and assume a purely saprophytic existence until such time as it gets the opportunity of exercising its powers again and completing its life-cycle as a parasite. Thus, in illustration of this view, Hueppe, writing on the subject of Asiatic Cholera, says that the specific organism, which has become parasitic during its stay in the intestine, can very readily adapt itself to a saprophytic existence outside the body; that it is virulent when it leaves the body and loses this virulence to a large extent during its stay in the soil, and not, as Pettenkofer says, non-virulent when it leaves the body and deriving virulence from the soil. On the other side, it has been urged that this view has nothing to support it and indeed is discredited by the fact that almost every epidemic can, if properly investigated, be traced to the incursion of infective material in the form of a case freshly imported into the community. Thus again, referring to cholera, Pettenkofer so far agrees with this contagionistic view that he believes that, at any rate where Europe is concerned, a new "einschleppung" is necessary for every fresh outbreak, and he thus disagrees with the autochthonist theory which is supported by Jules Guerin. But Pettenkofer, as a localist, demands something more than the mere presence of the specific organism, for the production of cholera. His views may be formulated thus,-

x = cholera germ, generally carried about by persons, clothing, etc.

y = time and place disposition,-porous, moist soil.

x plus y = z, the disease.

Naegeli, in his so-called "diblastic" theory to explain the spread of cholera, attempts to reconcile the views of localist and contagionist. According to him, for the infection of the healthy, a micro-organism from the sick is necessary which he calls "x" or the contagium; but to enable this to cause the disease, another germ from the locality,- as a rule, an infected soil,- is required to give the individual disposition to the person, and this he calls "y" or the miasma. The contagium, he says, can be carried about, but the miasma is not transportable.

x = the contagium,- a germ,- transportable.

y - the miasma,- a germ,- not transportable.

x plus y = z, the disease (cholera).

Whichever of these theories is nearer the truth, the practical lesson to be learned from them is of the utmost value to the epidemiologist in the prevention of disease and its spread. Small-pox remained a scourge until vaccination was introduced and now, although we may still be unable to prevent the disease-germ from spreading, we can, at any rate, make the individual members of a community sterile for that germ. Similarly, although it be not in our power to prevent the spread of the organism of cholera, yet we can make the locality sterile for it by draining and purifying the soil, improving house-drainage, removing pervious cess-pools, etc. It is on a consideration of the view which holds that organisms assumed to be the specific causes of these diseases are obligatory parasites possessing, however, the property of resisting external conditions for a certain time, that our methods for combating epidemic diseases are based. For, on the one hand, we resort to "isolation" to prevent further spread of the germ, while, on the other, we carry out "disinfection" with a view to destroying existing infective material. In the case of one of these diseases, small-pox, we have a prophylactic that is certain in its action, thanks to the work on vaccination by Jenner, which was brought to a practical issue in May, 1796, and the principle of which was subsequently confirmed by the extensive work done by Pasteur in the way of veterinary vaccination.

So far as the diseases of the second group are concerned, we have already drawn attention to their clinical and epidemiological characters and contrasted them in these respects with the maladies of the previous set. The specific causative organisms in each of these diseases, with the single exception of rabies, are known to us, and each organism fulfils the various requirements laid down by Koch and by Martin, in relation to its own disease. This being so, we are of course able to deal with the spread of these troubles if, for the present, not quite successfully in certain instances, still as a rule on more rational and scientific lines than in the case of diseases the precise nature of the causative agents of which we are not as yet familiar with, but can only surmise from analogy.

With regard to the small intermediate group comprising the two diseases, influenza and plague, the specific micro-organism has in the case of each, been isolated within recent years. The clinical characters vary considerably in the case of plague, perhaps less so in that of epidemic influenza vera (as differing from either endemo-epidemic influenza vera, or endemic influenza nostras, i.e. pseudo-influenza, catarrhal fever, "la grippe"). In its epidemiological features true epidemic influenza is characterised by its wideness of distribution, rapidity of diffusion, and shortness of stay in a given locality. So far as the epidemiological characters of plague are concerned, these will be made the subject of a special chapter and need therefore not be entered into at present.

Having dealt at some length with bacteria themselves in relation to epidemic diseases and their spread, we pass on to a consideration of another very interesting part of our subject, namely the rôle played by the bacterial products which constitute an important characteristic of bacterial activity. It is largely held at the present time that the manifestations of diseased conditions are the immediate result not of the presence of specific organisms themselves but of the complex substances produced by them during their period of growth and multiplication. For, while exercising their activity, bacteria set up fermentative processes, convert starch into sugar, proteids into peptones, and so on,- changes due to bacterial secretions termed "enzymes" or ferments. Again, as the result of their action on dead proteid matter, bacteria produce substances, more or less poisonous in their nature, called "ptomaines" which at one time were regarded almost universally as the agents that gave rise to the symptoms of many infectious disorders, although of late this idea has to a considerable extent been abandoned. As the result of further enquiry into the subject, aided by improved methods of investigation, in this department of chemistry, other poisonous substances, constituting the bacterial products of pathogenic microorganisms, have been detected which are neither enzymes nor ptomaines but yet have the power of giving rise, quite apart from the specific organisms themselves, to the characteristic symptoms of disease in a susceptible animal. To these poisonous products a very large number of names has been given, such as albuminoid substances, albumoses, tox-albumins, nucleo-albumins, proteins, nucleo-proteins, etc. The very fact that there is this great diversity in nomenclature, would indicate that the nature of these poisons is not as yet properly understood, and it has therefore been very rightly suggested that, as long as there is any doubt as to the real poisonous principles having been isolated, the generic term toxin or poison should be employed to indicate the substances in question. Now, it is noteworthy that these toxins can be artificially separated from the organisms that give rise to them, and that, if injected into susceptible animals during their lifetime, they can set up in them symptoms characteristic of the diseases of which they are respectively the specific causes, and can even produce a fatal result as is the case, for instance, with tetanus. A consideration of these facts gives the clue to the nature of what is known as the "incubation" period in infective disease. For, suppose the living germ of such a disease infects a susceptible individual, it grows at a rate which is characteristic of the particular organism but, during this time, the person feels no ill effects from the presence within him of the objectionable intruder. Nor do such ill effects manifest themselves until enough time has elapsed for a sufficiency of toxins to be formed to give rise to certain general symptoms the onset of which constitutes what has been termed the "invasion" of the disease. The incubation period then consists of the interval which elapses between infection on the one hand, and invasion or onset of the first constitutional symptoms on the other, and it corresponds accurately with the time taken by the germ to multiply and produce its toxins in sufficient quantity. The primary constitutional symptoms of invasion are, in their turn, followed by the specific symptoms or those characteristic of the disease in question. In connection with the nature of these poisons much discussion has arisen as to whether they are the direct products of the action of bacteria on the tissues or the outcome of the action of enzymes on the surrounding proteid matter, the enzymes themselves being the original products of activity of the micro-organisms. Thus, Buchner, in common with others, supports the former view, while Sidney Martin holds the latter, asserting in the case of diphtheria, for instance, that an enzyme or ferment is first produced by the bacillus and, in its turn, liberates toxins by acting chemically on the surrounding tissue-proteids. While it would be a matter of the greatest interest indeed to be able to decide whether these poisons are in reality chemical substances or are of the nature of ferments, it is of the utmost importance to consider what occurs practically when these toxic products are introduced into the system of a living animal. Laboratory experiments carried out with great precision, have done much to elucidate matters. Thus, it has been found that, given a suitable animal, small doses of a powerful toxin are capable of producing a lethal effect, and further, that an intoxication and death may result in a second animal inoculated from the first. Occasionally it has been noticed that, after inoculation with a small dose, the poison lies latent for a certain (incubation) period and then there comes a sudden and acute outburst of symptoms characteristic of the poison, illustrating a kind of progressive power which the toxin possesses. This leads one to entertain the idea that it is possible for infective disease to be handed on from person to person through the medium of the toxin alone without necessarily the presence of the specific organism for, if what has been described above takes place in experimental cases in the laboratory, it seems conceivable that, in a disease of a highly infectious nature, small doses of a toxin may pass from the affected to the susceptible and set up the trouble in the latter.

From the subject of susceptibility we naturally pass on to a consideration of "immunity", - a subject which has lent itself to endless controversy and, to explain the nature of which, numerous theories have been devised, all more or less plausible but none, so far, quite satisfactory. For instance, there is what has been called the "exhaustion" or "pabulum" theory, a view which assumes that the body contains a special and separate nutritive substance suited to the specific organism of each disease to which it is liable, as one disease can protect only against itself. Then there may be mentioned the "antidote" or "retention" theory whereby it is asserted that just as the yeast plant by living and growing in a saccharine fluid under suitable circumstances, produces a toxin, alcohol, which when it attains certain proportions, inhibits the further activity of the yeast, so a pathogenic organism in the course of its development produces a substance which is retained in the system and acts as an antidote to the further development of that germ in the same creature. But, in order to comprehend recent developments on the subject of immunity, a knowledge of Metchnikoff's work and theories is indispensable, and the best way to understand and appreciate this writer is to read carefully his volume on "Immunity in infectious diseases", published in 1901, which "sums up the labour of twenty-five years" and contains the latest and most mature expression of his views. The literature on immunity has of late years become appallingly extensive and complicated, partly owing to the intrinsic complexity of the subject, and partly from the confusion of an ever increasing jargon of newly coined technical terms. Metchnikoff, however, has the gift of expressing himself in terms intelligible to a wider audience than the inner circle of those actually immersed in some particular detail of research and controversy. The keynote of his doctrine is that "there is only one constant element in immunity, whether innate or acquired, and that is phagocytosis". One need hardly enter here into the very numerous and complicated details of this interesting subject as one is tempted to do after reading this masterly work, but it might be allowable just to touch, <u>en passant</u>, upon the leading features of Metchnikoff's theory. Phagocytes occur (1) partly in the circulation as (a) macrophages (large lymphocytes) with much non-granular protoplasm, and (b) microphages (polymorphonuclear leucocytes) with protoplasm containing granules either eosinophile, amphophile or neutrophile; (2) partly in the fixed tissues ("fixed" phagocytes) namely, in the spleen, endothelial and connective tissues, muscle fibres and neuroglia,- they are all macrophages, often closely resembling the free or circulating macrophages. The macrophages and microphages display a difference in their phagocytic activity, for the former seize and devour (1) material of animal origin, e.g. blood corpuscles, spermatozoa, etc., (2) infective micro-organisms of chronic disease, e.g. leprosy, tuberculosis, etc., and those of animal nature, e.g. the amoeboid parasites of malaria, the trypanosomata, etc., while the microphages destroy the bacteria of acute infection. There are corresponding differences in the soluble ferments or "cytases" (the "alexins" or "complements" of other writers) secreted by the phagocytes in the process of intracellular digestion, in other words, in the macro- and micro-cytases. These cytases or soluble ferments are essentially intracellular and they adhere with tenacity to the phagocytes which produce and contain them, until the latter are injured when they allow a part of their cytases to escape and thus impart to the serum the haemolytic and bactericidal properties which, according to Metchnikoff, were not originally present in the normal plasma. The phenomenon, according to him is closely comparable to the formation of fibrin ferment for, so long as the white corpuscles are intact, no fibrin-ferment is secreted by them, but when they are damaged, as in blood withdrawn from the animal body, fibrin-ferment is at once formed and coagulation sets in. He says that "the cytases rid the animal body of the micro-organisms without the slightest observable co-operation on the part of other soluble ferments". The factors at work in the case of acquired immunity are more complicated for here, as a general rule, there exist in addition to the micro-cytases other substances which play an important part in the defensive action of the animal organism against bacteria. These substances are termed "fixatives". They are not in themselves bactericidal, but by fixing themselves on the micro-organisms, they render the latter much more susceptible to the bactericidal action of the micro-cytases. These fixatives also belong to the group of soluble ferments but differ from the cytases in that they resist much higher temperatures for, whilst the latter are completely destroyed at 55°C., the fixatives must be heated to beyond 60°C. or 65°C. to be completely destroyed or altered. Again, fixatives manifest a high degree of specificity, for the majority of them are incapable of fixing themselves on more than a single species of bacteria or class of animal cells, whereas the same micro-cytases are able to attack all kinds of animal cells. Further, fixatives are not anchored to the cells producing them, but readily pass into the surrounding fluid and they may therefore be described as "humoral". Still Metchnikoff strongly insists on their cellular origin and quotes the work of Marx and Pfeiffer who found the specific fixative of cholera vibrios in the spleen, lymphatic glands and bone-marrow, at a period before any was present in the blood. He confidently asserts that the phagocytes are the particular cells which produce these fixatives and that these latter, being produced in superabundance as a consequence of the phagocytic stimulus, pass into the blood plasma and thence into the fluids of exudations. Metchnikoff says it is a misconception to think that his theory of acquired immunity is fundamentally opposed to the theory of "side-chains" or "receptors" formulated by Erlich, for the latter simply attempts to penetrate further into the mechanism of the phenomena observed as taking place between the micro-organism and the cell. He says "the act which we simply term intracellular digestion is divided by Erlich into its constituent parts. According to him there is a combination of the fixative, on the one hand with a molecule of the micro-organism, and on the other with that of the soluble ferment or cytase. According to Erlich, it is the amboceptors of the cells which become detached in order to furnish the fixatives that circulate in the plasma. For us there is simply an over-production of one of the two ferments of intracellular digestion, without defining more exactly what constituent part of this ferment passes into the circulation. The two theories may supplement each other but are in no way contradictory in principle". The one important point, however, in which they do not accord is, as Metchnikoff points out, that whereas the German authority believes that the cytases are always free in the body-fluids, Metchnikoff holds that they are only free in the animal during phagolysis and that under normal conditions they remain closely bound up with the phagocytes. While on this subject, we might call attention to the latest edition of Da Costa's work entitled "Clinical Haematology" which contains an admirable account of haemolysins as well as a very ingenious set of diagrams devised for the purpose of explaining the side-chain theory of Erlich and the modifications which it has had to undergo as a result of recent investigations. A very interesting paper on the subject of enzymes and haemolysins was read by Madsen at the 15th International Medical Congress held at Liston, 19th to 26th April, 1906.

So far we have considered merely the theoretical aspect of the subject and have entered somewhat fully into the very seductive subject of immunity, natural and acquired, and the theory which has of late years been elaborated by Metchnikoff. Let us now turn to the study of such practical results as have come about from the application of experimental laboratory methods. Suppose that a certain dose of a culture of a pathogenic organism, introduced into a susceptible animal, is productive of definite morbid phenomena and a fatal result, then a smaller quantity will set up only a slight local disturbance and a passing illness from which the animal will recover, while a still smaller dose will perhaps give rise to no bad effects at all. From this it follows that, in order to set up a disease artificially in an animal, a dose exceeding a certain limit must be administered, or in other words, that animals possess against disease powers of resistance or natural immunity to a degree indicated by, and directly in proportion to, the dose-limit which has to be exceeded in order to produce such disease, for the lower this limit the lower is the power of resistance or degree of natural immunity. The importance of this matter lies in the fact that it aids in explaining how it happens that occasionally the susceptible are exposed to infection and yet do not contract the disease. For apart from the possibility of such people, though exposed, having escaped the infection altogether, there is the point that owing to the smallness of dose the natural immunity was able to come to the fore and was sufficient to afford protection. Thus infection, dosage and immunity stand mutually related to one another. But the matter does not end here, for, in contradistinction to immunity or the positive power on the part of the tissues to resist infection, there is, so to speak, the negative power of "predisposition" that has to be taken into account. Thus the greater the susceptibility and the less the natural immunity in an animal, the smaller is the dose that will be necessary to produce a given infection; whereas, the less the susceptibility and the greater the natural powers of resistance, in other words, the more refractory an animal, the larger the dose that will be necessary. Or, it may be thus simply expressed, the dose required to produce a given infection is directly proportional to the degree of immunity which an animal possesses but indirectly so to the susceptibility. This however, is only so far as the natural powers of resistance go, for even a susceptible animal may be made to acquire such powers by the repeated introduction into its system of sublethal doses of the toxin, whereby the tissues are habituated or, as it were, educated up to withstanding larger amounts. Now, it frequently happens that organisms which have the power of producing disease, live an entirely saprophytic existence although placed under conditions that afford them numerous opportunities for becoming parasitic. That they do not take on the latter type under these circumstances, is to be explained by the fact that the tissues normally possess a degree of immunity or protective power against micro-organisms and the substances produced by them. This property may be in some measure natural, but it to a large extent an acquired habituation comparable to a tolerance of the most unfavourable climatic conditions which many people develop by dint of long residence in a locality. A further illustration of this faculty of habituation is to be found in the fact that the tissues of young animals are generally more prone to acquire infection than those of the same animals at a later age when their tissues have had time to become accustomed to various disease-producing influences. Again, with regard let us say to enteric fever as it occurs in the tropics, two points have been particularly noticed, (1) that it is alarmingly prevalent amongst young European soldiers and civilians in the East during the first two or three years after their arrival, and that the liability decreases with length of residence, and (2) that recent young European arrivals get enteric fever while the natives of tropical countries seemingly enjoy a comparative freedom from the disease. Writing on the first of these points, Manson says that "apparently a sort of acclimatisation, or rather habituation to the poison is established with time, just as tends to be the case with other organic poisons". With reference to the second point, Davidson expresses the opinion that it is an instance of new conditions increasing and the influence of habituity decreasing the liability to disease, as in the case of the young British soldier who goes to India, unaccustomed to a new set of pathogenic environments, and acquires enteric fever much more readily than the native Indian soldier does. Similar to this is the case of the native of a blackwater or haemoglobinuric fever country who remains immune or nearly so as long as he continues to reside in his native district, but loses his immunity to some extent when he goes to another part of the country. Again, under ordinary circumstances, a person is less liable to infection with pyogenic and other cocci which generally lodge on his own skin-surface than he is with foreign organisms from outside sources, for the tissues are habituated to the presence of the former. For example, in a skin incision little or no trouble follows the introduction of the cocci usually inhabiting the skin-surface, whereas when any foreign matter is introduced from without by the knife, there arise between the tissues and such matter sundry manifestations of a struggle or, in a single word, disease. Herein lies the principle which has to guide us in the practice of modern surgery where it is of greater importance by far to prevent the access to incisions of unclean matter from without than to try and render sterile the skin-surface through which an incision is to be made, for not only is the latter practically impossible, but it also tends to lower the resisting powers of the tissues of the part. Now, these defensive powers of the tissues are, as we have already seen, of the very highest utility and such that on the building up and strengthening of them is based a very important part of our system of treatment in many diseases, especially those in which medical science has not as yet placed a specific remedy in our hands, as for example tuberculosis in its various manifestations. It is these same powers of resistance in our tissues which guard us against the inimical action of the many bacteria of putrefaction which we normally harbour in our system, both on the external surface of our body and on such mucous membranes as that of our alimentary tract where they naturally play a very important rôle in our internal animal economy. During a state of health the living protoplasm of our tissues exerts a defensive power and resists any attempts on the part of these germs at leaving their usual habitat and invading the parts around, but if this faculty is weakened to any extent, as when the tissues are damaged or destroyed, the barrier or line of defence being removed, the organisms attack the damaged or dead protoplasm and exert their functions, with the result that putrefaction occurs. In this way it may happen that organisms like the bacillus coli communis, usually not only harmless but serving a very friendly and useful purpose, come to acquire pathogenic properties.

Next we go on to take up the consideration of a series of studies that have advanced very far of late years and have recently culminated in the establishing of the widespread and well-known methods of serum-treatment. For, while it was noticed on the one hand that the typical symptoms of a disease could, as we have already said, be produced by the introduction of toxins apart from their specific organisms, it was on the other hand also observed that immunity could be artificially produced or developed by the use of such toxins alone, not only against the action of repeated and larger doses of these toxins themselves, but also, <u>mirabile dictu</u>, against that of the living organisms from which these are formed. Moreover, it is a fact worthy of note that this immunity brought about by the use of toxins of exalted virulence and in increasing doses, may be developed to a high degree, and yet this can by no means go on indefinitely, for there is a limit, often a very sharp one, and any attempt to go beyond it will fail, causing the immunity to fall in degree and the animal to weaken and die. What happens artificially in a case of this kind appears to be analogous to that which takes place in the relapses met with in naturally acquired diseases like enteric fever, for as the patient appears to have got the better of the trouble and seems to be rapidly improving, there suddenly comes about a change in his condition with a return of the morbid symptoms. It has been suggested that this phenomenon is due to "renewed local irritation", but such an explanation does not satisfy the bacteriological view of the case. It appears much more reasonable to say that in such instances the machinery engaged in secreting the antitoxin suddenly breaks down as the result of the high pressure at which it has been working and that there occurs in consequence an increased metabolism or elimination of the antitoxin, allowing the bacteria, so long kept at bay, to have it all their own way now. The discovery that bacterial toxins possessed this remarkable power of imparting immunity against disease, was the starting point of much work on similar lines, and very soon the literature on bacteriology was flooded with the results of innumerable laboratory experiments. The value of work of this nature as done by scientific experimentalists like Von Behring and Kitasato, was soon realised when they first announced to the world their discovery that the blood-serum of animals artificially immunised against bacterial diseases by the use of toxins, possessed the power of annulling the toxins of these diseases, when injected into other animals, and thereby of protecting against such toxins. Their earliest labours in this direction were undertaken in connection with diphtheria and tetanus toxins, and they showed that the protection afforded by a serum obtained in this way was not only against the toxins but also extended to the specific organisms productive of such toxins; or, in other words, that a serum thus obtained would not only protect an animal against the toxins, say in the case of diphtheria, but would also afford it protection against the effects of inoculation with the living bacilli. The converse, however, does not always hold. Thus while, as Notter and Firth express it, "a serum which is anti-toxic is also anti-biotic", yet an anti-biotic serum is not necessarily anti-toxic. Whatever be the way in which the actual antitoxic substances in the serum are produced, if we consider first that the potency of the serum is roughly in proportion to the quantity of toxin introduced into the body, and secondly that the antitoxic property is specific,-in other words, that the antitoxin of one disease protects only against that disease, it is safe to say that the essential element in the production of the antitoxic substance in the serum is the presence of the bacterial toxin. It is, however, easier to immunise an animal to fatal doses of living organisms than to similar doses of their toxins, and the serum of animals thus rendered immune is protective against inoculation with living bacteria but not with their toxins. The whole subject is one of the greatest complexity. The manner in which these antitoxins act in establishing immunity is a point which, owing to the very intricacy of its nature, exerts a peculiar fascination on the student of such a subject, one which is still entirely in a state of theory. Let us then ask ourselves, what is a theory? It is a mental picture which we take to represent something that does not come directly under observation,- a picture that ought to be quite a definite one. Next, let us consider if any of the theories that are extant to explain the mode of action of these antitoxic substances, is satisfactory in all respects. First there is the suggestion made by the French school of scientists that antitoxins act by fortifying the body-cells against the toxins, working only _in vivo_ and not dealing in any way with the toxins themselves. This view does not seem satisfactory in so far as its first clause is concerned, as it offers to the mind no definite picture as to how the suggested fortification of the cells takes place. As for its second and third clauses the theory appears to gain support from the fact that Calmette, in a series of experiments, found that snake venom did not lose its toxicity when brought in contact with antivenin *in vitro*. Antivenin was mixed with venom *in vitro* and, after it had been in contact with it for a certain time, was destroyed by exposure to heat at 70°C, a temperature which did not affect the venom. The fact that the venom had not been altered by contact with the antivenin under these circumstances was demonstrated by the results of a subsequent injection of the heated mixture of venom and antivenin into a rabbit. Secondly, we have Erlich's theory that antitoxins act directly on toxins, both *in vitro* and *in vivo*, combining with them in accordance with the laws of chemical equivalence. This explanation was suggested to him by an observation of the following facts, (a) that if x c.c. of toxin are neutralised by y c.c. of antitoxin, it will require 100 times y c.c. of the latter to neutralise 100 times x c.c. of the former, (b) that C.J.Martin, of Melbourne, demonstrated that in Calmette's experiment described above, the venom was destroyed *in vitro* if contact with the antivenin was sufficiently prolonged, (c) that the same Martin showed that the diphtheria toxin which can be separated by filtration from a recently made mixture of the diphtheria toxin and antitoxin, cannot be recovered from such a mixture after the lapse of a certain period, the toxins having probably combined with the albuminous antitoxins whose molecules are too large to pass through the pores of the gelatine filter employed, and (d) that Erlich, working with ricin, showed that the agglutinating and dissolving action which this substance exerts on the red blood corpuscles, is abolished when the ricin has been previously mixed for a few minutes _in vitro_ with its corresponding antitoxin, namely antiricin; the mixture of the two which has stood for a while is a fluid neutral in respect of its action on red blood cells, as a chemical combination has occurred between the toxin and the antitoxin. Thus, it appears manifest that the theory put forward by Erlich is the most acceptable one regarding the mode of action of antitoxins, substances which may therefore be said to be toxi-tropic in their nature, that is, having an affinity for toxins and combining chemically with them, both _in vitro_ and _in vivo_, provided the contact is long enough and the temperature and other conditions are also suitable.

The way in which these toxins are produced on the introduction into the system of substances of an exceedingly complex and frequently unknown chemical structure, is a point still under debate, and the most generally accepted views have already been briefly alluded to. It can evidently not be a provision made for the preservation of the species, as antitoxins are not produced for all poisons indifferently; nor are they produced in animals injected with any of the alkaloids or mineral poisons, but only after the introduction into the system of poisons of an albuminous nature, such for instance as certain bacterial toxins e.g. diphthero-toxin, tetano-toxin, etc.,and poisonous vegetable albumins e.g. abrin, ricin, robinin, etc. Antitoxins are therefore also albumino-tropic or proteino-tropic substances. The cells which produce them are, according to the theory propounded by Erlich, those containing in their protoplasm, what he terms the "haptophoric groups" or "side-chains" which possess the property of grasping and embodying albuminous substances. As an objection to this theory the question has been raised as to whether, say in the case of tetanus, so much antitoxin can be produced by the few cells attacked by the tetanus toxin. In connection with this subject it may be pointed out that poisons of the kind we are considering, are either mono-tropic (e.g. tetanus toxin which acts only on the central nervous system), or poly-tropic. If tetanus toxin is introduced into the system viâ the skin, a hundred times the quantity is necessary to produce the same effect as when it is injected directly into the central nervous system, so that it has been said that ninety-nine parts are spent on cells other than those of the central nervous system. The clinician admits that poisons attack probably more cells than he knows anything about. It has been observed that insusceptible animals, owing to a distribution of the poison in their system, yield much antitoxin as compared with susceptible animals which produce little inasmuch as the poison at once attacks some vital part. The observation of the fact that, in addition to a protective action, the blood-serum of immunised animals possessed also a curative power and was able to arrest the process of disease though fully established, completed the work that resulted in the triumphant discovery of the principles of serum-therapy.

Before leaving the subject of immunity and the application of its principles in the management of disease, it may not be out of place to refer briefly to Behring's recent work in this direction, with the results of which he thought he would startle the world when he published these in 1905. It was in regard to the terrible scourge, tuberculosis, that Behring believed a cure could be obtained on the plan of establishing a "cellular" immunity in contradistinction to the "humoral" immunity conferred by an antitoxin. This cellular immunity is gained, according to him, by an organism through its cells being impregnated, in the case of tuberculosis with a substance called by him TC, which exists in the bodies of tubercle bacilli. This TC has manifold properties, as implied in the general terms formative, fermentative and assimilative, and is the "quasi-vital principle" of the bacilli. In immunising cattle against tuberculosis, TC combines with the tissue-cells, especially those of lymphatic germinal centres. It is the cause of the reaction to tuberculin as well as of the acquired protection against tuberculosis. Starting from the proposition that to introduce tubercle bacilli into the human body is inadmissible, the problem which Behring set himself was to spare the organism the labour of elaborating TC (and acquiring active immunity) by isolating TC <u>in vitro</u> and employing it to confer passive immunity. According to him, in tubercle bacilli there are three groups of bacillary substances distinguishable, of which two are highly toxic and one inert. They are (1) TV, soluble only in pure water,- fermentative and catalytic,- to which are due the toxic effects of Koch's tuberculin (one gramme of dry TV is more toxic than one litre of Koch's original tuberculin), (2) TGL, a globulin, soluble only in neutral saline solutions and also toxic, and (3) several non-toxic substances, soluble only in alcohol, ether or chloroform. After these substances have been extracted, the bacilli retain their shape and staining reaction and are called "rest-bacilli". They contain TC and can be converted into an amorphous substance, TX, which on inoculation impregnates the lymphatic cells of the animal, the cells themselves becoming oxyphile in the process, while, <u>pari passu</u> with this metamorphosis, immunity develops. These observa- have so far been limited to animal experiments and it only remains to add, in order to complete the description of TC, that it possesses the curious property of evoking tuberculous granulations which, however, never caseate or soften. This is the tenour of Behring's communication.

Now to pass on to the development that followed next upon the establishment of serum-therapeutics, we must allude to the discovery of the fact that the serum of artificially immunised animals possesses, in addition to the curative powers mentioned, a further remarkable and characteristic effect on the living organisms of disease and, moreover, that the action is a specific one. This property of antitoxic sera may be found manifested in cases of disease naturally acquired, at quite an early stage, and the discovery of this circumstance was at once utilised as a means of diagnosis, now generally known as "serum-diagnosis". The method is employed in order to make out the nature of a disease, on the principle that the blood of men or animals suffering from a specific disease, possesses the power of agglutinating and sedimenting the bacteria causally associated with that disease. This means of early diagnosing the nature of a complaint, has already been made use of in many diseases, such as Malta or Mediterranean fever, bacillary dysentery and especially enteric fever in detecting which it is of the utmost value. G. Jochmann (Deut. med. Woch., May 17th, 1906) describes a series of experiments which he carried out with Weichselbaum's organism in connection with the serum-diagnosis and serum-therapy of cerebro-spinal fever; he obtained a polyvalent serum which, according to him, rendered it easy to distinguish between the true Weichselbaum cocci and similar micro-organisms, among which he mentions a Gram-negative coccus. He does not express a definite opinion as to the curative value of the serum after the limited test he has been able to give it, but he is inclined to think it does good and advises its prophylactic injection in 20 c.c. doses under certain conditions. We have said that the action is a specific one, for not only will the blood-serum of an animal suffering from one disease not act with the organisms causing a totally different ailment, but then, in the same group of disorders e.g. bacillary dysentery, the serum from a case due to one variety of bacillus dysenteriae, let us say Flexner's, will not act with a culture of another bacillus productive of dysentery, as for example Shiga's bacillus, and the converse holds good as well. In addition to the method being applicable to the diagnosis of disease at an early stage, it can also be employed in a purely bacteriological manner for the purpose of recognising or, as it were,"diagnosing" a culture of an unknown organism or in order to confirm a suspicion as to its nature by noting the disease with the blood-serum of which the organism will agglutinate or sediment. It is not necessary for the serum, in order to produce the effects that have been described, to be taken from the blood of one actually suffering from the disease, for the blood of an animal immunised against a specific malady possesses identically the same power as that of one suffering from the disease at the time.

The whole subject concerning the use of the serum of immunised animals in the diagnosis and in the prevention of specific infective disease by the conferring of immunity against it, is one which is still in its infancy but which promises fair to make great and rapid advances. For instance, in the matter of granting protection against the ravages of disease, much practical work has already been successfully carried out in the veterinary department, especially in various parts of South Africa and on the east coast of that continent where it has been found impossible to preserve old and import new stock owing to the deadly effects of cattle-plague or rinderpest, also known as typhus contagiosus, steppe disease, steppe murrain, peste boum (not to be mistaken for Yersin's "peste bovine") and, in India, as "mán", besides redwater fever and numerous other troubles of a like nature. Much good work has lately been done on these lines by Koch and others. Very important is the subject of the immunising of cattle in places where such fatal diseases are rife and very distinct the advantages to life in the case of animals that have acquired an immunity, as compared with those which have not, e.g. fresh importations into the country. Indeed in veterinary phraseology distinction has been drawn between the two sets by means of the terms "salted" and "clean" respectively. Nor is the work done of late years, so far as similar diseases affecting man are concerned, any less important considering such discoveries as those of Behring's anti-diphtheritic serum, the anti-streptococcic serum, and Yersin's anti-pest serum which in addition to being a preventive, has been said also to be a curative provided it is suitably administered as was done in the cases of plague that occurred at Leith some half a dozen years ago and again in a set of 26 cases in China of which 24 were saved, according to report by this mode of treatment. We shall have occasion to consider Yersin's anti-pest serum at greater length later on in the course of this work.

The practical application of a knowledge of these numerous facts brought to light by the science of bacteriology, affords a vast field for the work of the epidemiologist in the prevention of disease and its spread. Taking into account only those troubles which are known to be associated with a bacterial causation and the organisms of which conform in all respects to Koch's postulates, we find ourselves at once confronted with a considerable number which, though they may vary clinically and in other respects, have certain points in common. Thus, besides being of proved bacterial origin, they have their organisms generally present in the blood, capable of causing analogous lesions in other animals, recoverable from those animals and capable of cultivation outside the body, the pure cultures being of such a nature that, if inoculated into other susceptible animals, they will produce the disease in such a way that from the morbid tissues the organism can again be recovered. Such diseases belong to the second of the groups which we distinguished at an early part of this chapter, and in some of them e.g. anthrax, tetanus and diphtheria, the identity of the toxins of artificial cultures and of those obtained from the diseased tissues, has been demonstrated by Martin. There are, on the other hand, diseases of undoubted bacterial origin in which the suspected organism does not conform to all these requirements, as for instance leprosy in which it has not yet been clearly shown that the organism can be grown outside the body and in connection with which the inoculation with leprous material has so far not succeeded in imparting the disease. Manson says that "many attempts have been made to communicate leprosy to man by inoculation; hitherto, with one exception, all have failed". Again, the specific organism of influenza has been found and cultivated outside the body, yet the results of animal experiments remain incomplete. Similarly, in the case of enteric fever, we are familiar with the specific germ and can cultivate it on artificial media, but still no clear proof has hitherto been given of the transmissibility of this disease to animals. Regarding this, Osler says that "the production of the disease experimentally by the cultures has not yet been met. Probably the animals used for experimentation are not susceptible to typhoid fever". Still such an expression as "bovine enteric" is occasionally met with in the literature of the day and the "possibility of the transmission of enteric fever from men to animals, and vice versa, must not be overlooked". Further, as already pointed out, there are instances of disease in which various organisms may be concerned, each capable of causing the same lesions and similar clinical symptoms, as for example septicaemia or pyaemia, indistinguishable in clinical features even though caused by any of the different forms of pyogenic cocci. Again, the same organism, let us say the diplococcus pneumoniae, may give rise on the one hand to a disease like lobar pneumonia with general symptoms, or on the other to purely local lesions, suppurative in type, thus warranting the conclusion that the term "pneumonia" ought to be looked upon as a general one including several different forms of inflammatory disease. In connection with certain other diseases, of the first group, e.g. small-pox, scarlet fever, etc., although many organisms have been described from time to time, we require still further evidence before we can really accept these as the genuine causae causantes, while in yet another set of troubles no causative germs have hitherto been discovered although, from analogy, we can have no doubt whatsoever as to the organismal nature of their origin, as in the case of rabies where, however, bacteriological methods have fortunately stepped in and triumphed by the production of a protective substance in the form of an attenuated virus.

There are certain cases in which a disease, in support of the specific nature of its origin, conforms in the strictest manner possible to the requirements of bacteriology and responds as rigidly to the serum test, and yet its specific nature is doubted by some. An example of such a disease is diphtheria. It is said that inasmuch as (1) the diphtheria bacillus is sometimes to be found in throats not pronounced by the clinician to be diphtheritic, and (2) the diphtheria bacillus is often not discovered in cases which are clinically diagnosed as diphtheria, evidence of the specificity of the organism is wanting. With regard to the first objection, all physicians of clinical experience allow that the difficulty of diagnosing the disease is at times very great indeed, in the absence of bacteriological methods; therefore, in such instances, if the organism is discovered in the throat, clinical diffidence must give way to bacteriological evidence and the case must be looked upon as one of the genuine disease. With regard to the second point, the non-discovery of the germ may be due either to a misdiagnosis of the case at the bedside (the case not being really one of diphtheria at all), or to want of skill or care on the part of the bacteriologist, for the sources of fallacy are numerous indeed, especially in the hands of the inexperienced worker in bacteriological methods involving such delicate manipulations and technique. Negative results in such researches are of little value unless amply confirmed, for it is absurd to say that because no diphtheria bacillus is found in a particular throat the case is not one of diphtheria. Not only has the organism been found in throats long after convalescence has set in, but it has also been detected in those that appeared to be normal, a bacteriological fact having a very important epidemiological bearing, as it shows how the disease may be kept up, as well as the unexpected sources from which danger of spread may arise. It indicates clearly the utility of antiseptic mouth-washes and gargles, far into convalescence. Considering the possibility that throats apparently normal may harbour the germ and act as foci for the spread of the disease, there arises a very important and special point associated with school-hygiene, suggesting the desirability of the regular medical inspection of school children, a system largely carried out in Germany. With reference to the special incidence of this disease in schools, Thorne Thorne says "apart from age and susceptibility, school influence, so-called, tends to foster, diffuse and enhance the potency of diphtheria, and this, in part at least, by the aggregation of children suffering from that sore-throat which is prevalent antecedent to, and concurrently with true diphtheria". It has been estimated that in certain at least of the counties of England, the school authorities have daily charge of about one-fifth of the whole population and that the most susceptible to infectious diseases. Hence the object to be aimed at is complete and prompt co-operation between school and sanitary authorities, which ought to be of the utmost benefit to both. School attendance being compulsory, educational authorities cannot escape this obvious responsibility. In suggesting the performance by the county authorities, of this pure and simple public health work, the Committee on Physical Deterioration, in par. 326 of their Report, say "that bringing the sanitary administration of the county into touch with the schools may lead to the anticipation and prevention of many of those epidemics which are now a fertile source of local expense". The medical inspection of school children, apart from that of the teaching staff and others and in addition to the sanitary supervision of schools and the instruction in hygiene of teachers and scholars, is the method now being very highly and rightly advocated. To return to our discourse, however, although much has been written on the various modified, attenuated and analogous forms of the Klebs-Löffler bacillus, there is nothing in the literature on all this subject which weighs in the slightest degree against the specific relationship of this micro-organism to diphtheria. The point of special interest to the epidemiologist is that, being a disease of low degree of infectiousness, transferred probably only by means of infected mucous secretions, and not occurring in the lower animals with the exception of the cat, diphtheria is still on the increase in England as compared with its original home, France; in the same way scarlet fever has, as it were, removed its favourite haunts from England to France. Newsholme has contributed some very interesting matter to the literature on this subject and has gone largely into the statistical aspect of the question. Moreover, the disease from being one of rural areas, has of late years in England, at any rate, established itself in towns. Milk is a suitable vehicle for the conveyance of the infection, and the responsibility for some outbreaks has been thrown on cows. It has been suggested that an ectanthropic existence of the germ, in a manner not yet discovered, is another possible factor in the spread of the trouble.

An interesting disease, from the point of view of relation of bacteriology to epidemiology, is enteric fever. A very great deal could be written on this interesting subject in review of the opinions expressed from time to time by such authorities as Murchison, the founder of the well-known "pythogenic theory", an autochthonistic, soil or localisation theory which holds that the disease can be produced _de novo_ by insanitary surroundings and especially products of putrefactive and fermentative processes occurring in filth and excrementitious matter not mixed with typhoid dejecta; or sewer gas, or the mixture of excreta, not derived from a previous case of typhoid, with drinking water; and that the disease is not necessarily due to the existence of any specific germ. Buhl adopted a view whereby he struck a relationship of an indirect nature between the fluctuations of the ground water and the extent or intensity of enteric fever. Pettenkofer took up the position of a localist, associating the origin and spread of enteric fever with local, seasonal and personal conditions and believing that the infective matter resided in the soil, matured there and derived virulence thereby. At the present time, of course, no one doubts the specific relationship between the Eberth-Gaffky bacillus and this disease. Even though, as stated before, the typical disease has not yet been produced experimentally in the lower animals, its occurrence in them must be kept in view as a possibility all the same. By way of an objection raised against the relationship in this case, of germ to disease, now generally believed to be specific, it has been urged that the organism is seldom actually discovered in waters suspected of causing outbreaks of the disease. In answer to this, however, it may be stated that, taking into consideration the difficulties of isolating such organisms by bacteriological methods, the large volumes of water dealt with and the long incubation of the disorder, it would indeed be very surprising if the organism were constantly found. Nor must it be forgotten that, although the germ itself be not discovered, bacteriological and chemical proof of sewage-pollution is constantly forthcoming. That the disease is a water-borne one is, at the present time, a generally accepted fact. The discovery of the bacillus typhosus at the height of an epidemic may be a matter of interest to the bacteriologist, but it is of less interest and little importance to the epidemiologist than is the carrying out of such measures as will protect water-supplies from future contamination. As the virus is water-borne, it is easy to understand how it comes, every now and again, to infect such food-stuffs as milk, vegetables (watercress, etc.), also shell-fish (oysters), etc. A knowledge of these facts supplied by the study of the bacteriology of the disease, gives us the clue to the lines on which we have to work in order to prevent or stamp out epidemics of enteric fever. The proper selection of a source of water-supply, its protection and careful storage, and the directing of the sewage into harmless channels are some of the preventive measures indicated. The early recognition of the trouble when it does break out, is aided by the method of serum-diagnosis,- a plan which stood that able investigator, Dr Davies, in such good stead in the milk epidemic that occurred a few years ago at Clifton.

In the case of influenza, restricting the term here to the forms which Leichtenstern, in a very convenient classification, calls epidemic influenza vera and endemo-epidemic influenza vera, the specific organism was discovered by Pfeiffer and named after him. Bacteriology has not helped us much with methods for the diagnosis and practical management of the disease, and this still remains a great scourge, chiefly on account of its being very highly infectious in its nature and a disorder in which the patient, being able frequently to get about, resents proper methods of isolation.

On the specific relationship between the tubercle bacillus discovered in 1882, by Koch (Berliner klinische Wochenschrift, 1882) and tuberculosis, there is, at the present day, of course no shadow of doubt. Innumerable attempts have of late years been made to hit upon some method of treating the various manifestations of this disease by means of extracts of the bacilli and their products and, more recently, by serum methods, but so far without success. The names of Marmorek, Behring, and several others are honourably associated with such work. The results of the latest researches on this subject by von Behring have already been mentioned, and the account of his endeavours gives some idea of the intricacies and difficulties involved in such an undertaking. In the "Berliner klinische Wochenschrift" for January 22nd, 1906, the therapeutic value of Marmorek's serum is very ably discussed. In one article the report of Drs E. Stadelmann and A. Benfey is quite unfavourable to the use of the preparation. These experimentalists have tried the use of the serum in various cases of pulmonary tuberculosis, according to both the original plan and the modified methods advised by Marmorek, but in no case with any improvement. In another article there is an account of the experimental and clinical studies of Dr Ernst Levin, of Stockholm, made with a view to test the value of the serum. The opinion of this observer, based on the results obtained by the use of the preparation in a series of cases from various parts of Scandinavia, is distinctly favourable. He says that the serum is not sufficiently potent to absolutely prevent the development of tuberculosis, but that it has the power of neutralising tuberculous toxin and retarding the action of the tubercle bacillus on the animal organism and that therefore it is undoubtedly of therapeutic value. Tuberculosis is chronic in its nature, imparts no immunity and involves two factors, (a) predisposition, the personal element, a plastic factor which can be lessened and sometimes almost nullified by proper management, thus making recovery practically possible in some cases, and (b) the activity of the specific bacilli themselves. The ubiquitous nature of the organism and the numerous chances of infection render the hope of escape very slight indeed for those in whom the predisposition is well marked. The germ appears to flourish well as a saprophyte, though less virulently in this state and requiring passage through several animals ere it can again become fully parasitic. The bacteriology of the disease teaches that sanitary measures such as prevention of overcrowding, the securing of proper ventilation, good food, and, above all, healthy, open-air exercise are the most important desiderata both in controlling the spread of the germ and in combating the predisposition to the disease. Tuberculous meat and milk are still regarded as fertile sources of infection, by most authorities who advocate not merely such temporary measures as the proper cooking of the former and boiling of the latter, but the more radical plans of destroying diseased meat and of preventing the sale or use of milk from affected cows. On the recently much debated question of the relation of human to bovine tuberculosis, a great deal has already been said and written. Professor Dr H.Kossel, of Giessen, read a most interesting paper in German at the Paris Congress on Tuberculosis, in 1905. He distinguishes two types of tubercle bacilli, the typus humanus and the typus bovinus, and holds (1) that the tuberculosis of cattle is due to infection with tubercle bacilli of the typus bovinus, (2) that the tuberculosis of human beings arises chiefly from infection with tubercle bacilli of the typus humanus, transmissible from man to man, (3) that tuberculous lesions in human beings can be produced by the organisms of the typus bovinus, (4) that the tubercle bacilli of the typus bovinus can be transmitted to human beings by food derived from tuberculous animals, especially by the milk of cows affected with tuberculosis of the udder, and (5) that the part played by infection from bovine sources in spreading tuberculosis in man, is small in comparison with the danger threatening from a consumptive human being. Dr Nathan Raw, writing to the British Medical Journal of August 18th, 1906, on this very subject, and in continuation of previous articles written during the three preceding years, points out very well that "the intricate and difficult problem as to the exact relationship between human and bovine tuberculosis is still unsolved, because the actual test, viz. the experimental test of inoculating humans is inapplicable, and always will be. Hence we must work by roundabout methods, making clinical observation our basis, and relying on inferences from analogy, pathological research, and minute and careful comparisons between the bacilli of various origins for our ultimate conclusions". His view is that human and bovine bacilli are divisible into two distinct types of a common species, (1) typus humanus, and (2) typus bovinus, the different characteristics of which are the result of long-continued residence in a particular host. The opinion at which he arrives, at the conclusion of a very excellent note, is based, as he says "almost exclusively on clinical and pathological evidence", and it expresses the belief that "human and bovine tuberculosis are distinct varieties of disease, but that the human body is susceptible to both, and especially to bovine tuberculosis in the milk-drinking period of life". Ever since Villemin, by his classical researches, definitely proved that tuberculosis was an infectious disease, the relation between human and animal tuberculosis has been the subject of much investigation. It is, however, only since the time of Koch's discovery of the specific organism that comparative studies have come to be possible. In 1896 and 1898, Theobald Smith objected to the identity of the organisms concerned in human tuberculosis and in the "perlsucht" of bovine animals, on the ground of morphological differences in artificial cultures, as well as of differences in virulence on small animals. Koch and Schutz later on stated their belief that the bacilli from the two sources differed and that those derived from man could not produce tuberculosis in cattle. In an address recently delivered at Stockholm, Professor Koch reiterates his conviction that human tuberculosis is distinct from the bovine disease, and that the danger of human infection from the bovine is so small that, from the standpoint of public health, it may be disregarded. (Deut. med. Woch., January 18th, 1906). For the spread of the human disease he blames the laryngeal and pulmonary forms of the malady in which, as differing from all other forms of the trouble, the bacilli are excreted with the sputum and find free escape into the environment. He strongly urges notification and, so far as possible, hospital isolation especially in the more advanced and therefore more dangerous cases. He also draws attention to the value of sanatorium treatment for the early stages of the disease and, in the matter of the precautions necessary to be taken to prevent the dissemination of infective material, he strongly recommends the general adoption of a system on the same lines as are followed in Edinburgh and in Manchester. It is remarkable that while Koch holds that human and bovine tuberculosis are separate and distinct diseases, and that bovine tuberculosis if conveyed to man cannot set up generalised human tuberculosis and that direct infection from person to person is by far the commonest cause of the spread of the disease, Behring has views which are diametrically opposed to these. The latter maintains that human and bovine tuberculosis are the same disease, that nearly all tuberculosis is the result of infection during infancy by means of infected milk, and that direct infection from one person to another is not proved. Less recently Sharman and Lamkin recorded their opinions on "the relationship between human and bovine tuberculosis", in 1894, and Nocard published his views on "Animal tuberculosis and its relation to human tuberculosis" in 1895. The names of numerous other eminent and scientific workers, in addition to those already mentioned, are associated with valuable research on this subject, such as, Arloing, Bang, Baumgarten, Cornet, De Jong, Hamilton, Herzog, Heuss, Lignieres, Meyer, Moeller, Thomassen, Weber, Westenhoeffer, Young and a veritable host of others. The whole matter os one of the very first importance from the point of view both of purely scientific bacteriology, and of the more practical subject of prevention. Apropos the study of tuberculosis, it might be worth referring briefly to a recent, somewhat fashionable advance made in the scientific aspect of the subject. The allusion is to what has been named the "opsonic power" in tuberculosis, a knowledge of which is very desirable so far that at the present day, it is impossible to enter a bacteriological laboratory without hearing this subject discussed. "Opsonins" is a term invented by Professor, now Sir A.E.Wright to denote substances which are contained in the serum or plasma of the blood and which possess the power of influencing bacteria so as to render them an easier prey to the attacks of leucocytes. This power, known as the opsonic power, is present in the blood of all persons, healthy or diseased, but though approximately the same in normal persons, it shows variations amongst the diseased. The degree of opsonic power in relation to tubercle bacilli is found by mixing a small quantity of the serum to be tested with equal parts of (1)an emulsion of tubercle bacilli, and (2) blood corpuscles washed in a 0.5 per cent solution of sodium citrate in normal saline. This mixture is incubated for twenty minutes, then films are made and stained for the bacilli. The average number of tubercle bacilli ingested by the polynuclear leucocytes gives the phagocytic index, and from this is calculated the opsonic power. The index obtained with normal serum being taken as the standard and called the unit, the opsonic power of the serum of persons suffering from tuberculosis is expressed in terms of this standard. The work on this subject has not advanced far enough to warrant any opinion on its probable ultimate value to the clinician. It it, however, a point of scientific interest and importance, and we have included a short account of it here because, as recently as 1904, the significance of opsonins was discussed at Oxford by a body of scientific medical men, when the bearing of these substances on the fundamental problem of immunity was pointed out by Dr Bulloch. With some workers there is a tendency to the belief that in the estimation of the opsonic index we may have a means for the diagnosing of tuberculosis.

On another important disease, Asiatic cholera, volumes might be written, even though the subject be dealt with only from the restricted point of view of the relation of its bacteriology to its epidemiology. Since the discovery of the specific germ by Koch, in

Egypt in 1883, and subsequently in India in 1884, the science of bacteriology has taught us much regarding the nature and habitat of the organism, much that serves to guide us in the practical management of the disease both in its endemic form and during its epidemic prevalence. For instance, we have come to learn that on artificial media the organism grows best at blood-heat; that inasmuch as the growth of the germ is arrested under 66°F. (18°8 C), the disease dies out in winter in temperate climates, although the organism is not killed by the cold; that it is readily destroyed by desiccation and hence epidemics die down during the protracted dry season in many subtropical countries as, for instance, the Punjab where outbreaks flourish only during the rains. Further, we are now aware that cholera can be endemic only in regions where the winter temperature is not below 60°F. (15°5 C) and where the soil retains sufficient moisture all the year round, as for example, the delta of the Ganges; that the vibrio is destroyed by saprophytes in undiluted sewage and in the soil, whereas some species of torulae, sarcinae and colon bacilli promote cholera infection. Again, we know that the germ is found in the stools of cholera patients, that it has been discovered also in the dejecta of convalescents for as many as fifty days after the attack, and even in the faecal discharges of healthy persons who have been in attendance on cases of cholera; and that occasionally its presence has been detected in the gall-bladder and bile-ducts, and in rare cases in the vomit. Therefore for a widespread epidemic of cholera the following conditions are necessary, according to Davidson as well as most other modern authorities, (1) the presence of the vibrio which, in non-endemic areas, must be introduced from without; (2) a suitable medium for its growth outside the body, for it is not actually the vibrios grown in the intestinal canal of the sick that are the source of the infection, but the progeny of these grown in some medium outside the body; (3) a temperature above 60°F. (15°5 C); (4) a certain degree of moisture; (5) a vehicle by which it may be conveyed into the system, such as water, milk, other food and, in some exceptional cases, according to Davidson, the breathing air; (6) a susceptibility on the part of the population (thus, a severe epidemic may confer an immunity lasting for three or four years); and (7) a means of transport from place to place, such as persons suffering or convalescent from cholera, those who have been in contact with cholera patients and those who harbour the vibrio in consequence, clothing soiled with cholera discharges, cholera-polluted rivers and infected ships. According to Osler, the disease is not highly contagious, and infection through the air is not to be much dreaded, since the germs, when dried, die rapidly. Macpherson thinks that cholera has been epidemic in India since the earliest times, but the more recent view, supported by Koch and others, is that although this disease has been known in India for many hundred years, yet it was only in 1817 that it first, as it were, broke out of bounds and suddenly took on an epidemic type. The reason for this sudden change of form has never been clearly made out, and it still remains one of the mysteries of epidemiology. The cholera germ can live a saprophytic life almost everywhere and it has been shown to exist for as many as eighty-one days in the sewage-polluted water of Marseilles harbour. It is with reluctance we desist from going further into a discussion of the views expressed from time to time by the many famous writers on the subject. Leading amongst these may be mentioned the names of men like Petterkofer who adopted the views of the localist section of those whom he termed "ephodists", that is those who believed that the specific organism always required to be imported afresh into a locality. Then there is Jules Guerin who, from his writings, appears to have taken up the autochthonist view (vide Bulletin de l'Academie de Medicine, 1883, and his account of Cholera in Paris, 1884). He is also responsible for the idea of the "constitution medicale", a condition associated with the occurrence of the disease. Cunningham did much useful work on the subject. Some of Naegeli's opinions have already been mentioned. Rochard and Leon Colin contributed very largely to the literature on the epidemiology of cholera. Bouchardt regarded the disease as contagious and believed in the "foyers intenses", quoting in support of this the case of the Salpetriere epidemic of 1849. The Report of the Marseilles Commission well repays perusal, as also do the writings of M.Marey, the great exponent of the water-borne nature of the disease. Hueppe's views have already been briefly recounted. With regard to the ready manner in which the organism adapts itself to a saprophytic existence, outside the body, with a loss of virulence, Hueppe points out that the germ becomes more resistant in virtue of either a thicker membrane or zooglea or arthrospore (resting spore) formation. Regarding other workers on the subject, their name is legion, and it is unnecessary to go further into this matter here and either recite a list of names or indulge in the description of epidemics from the classical one of 1849 in Southwark and that of 1854 in Golden Square, investigated by Dr Snow, down to the outbreak that occurred in Hamburg and Altona, in 1905, the spread of the infection having taken place in this instance from the Austrian province of Galicia, via the rivers Vistula, Brahe, the Bromberg canal, Netze, Warthe, Oder, and by means of a canal to the river Spree and so on.

These are only a few of the most interesting points regarding some of the infective diseases, intended to illustrate the manner in which bacteriology is related to epidemiology, as well as that in which the more theoretical teachings of the former may be applied to the practical side of the latter. Were we to enter even briefly into such points in connection with each of the ills of an infective nature that "flesh is heir to" and the bacteriological aspect of which has been studied to any extent, and were we just to touch upon the practical uses to which these studies have been put in dealing with the endemic prevalence and epidemic extension of such diseases, this subject alone would fill up an entire work and would include a great many troubles that scourge mankind, also the enormous advances made within recent years in the study of their bacteriology and the manner in which these have been applied in the practical management of outbreaks of such diseases. It would take into its scope an account of the various methods of preventive inoculation and vaccination employed in human ailments and would include the study of epizootics and the forms of veterinary vaccination that have been so well worked up and so extensively employed of late. The infective diseases occurring in man are frequently so closely associated with certain troubles affecting the lower animals, that a study of the latter can no longer be neglected by the scientific epidemiologist, any more than the study of comparative anatomy can be disregarded by the intelligent student of human anatomy. Nay more, for if the diseases of lower animals are to be studied rationally, a knowledge of those animals themselves, of their morphology and life-history including habits and habitats, must first be acquired. To put it briefly, it means that henceforth the student of medicine must be a naturalist ere he can hope to be a scientific epidemiologist, pathologist, or even a capable practitioner. And if this applies to medicine in general, it does so very particularly indeed to that section of medicine which deals with such endemic and epidemic diseases as prevail in the tropics and subtropics. For who can gauge the richness in flora and fauna, of the tropical world? That the study of natural history from the point of view we have indicated is absolutely essential to scientist, epidemiologist, pathologist and physician alike, in dealing intelligently with disease, can be plentifully illustrated. Thus, how can one cope with malaria in anything like a rational manner without knowing about the protozoon that causes it and the insect that carries it about? Or again, how can one hope to be able to deal with the various forms of that interesting set of conditions comprised in the term trypanosomiasis, without being acquainted with the different varieties of the class of protozoa, known as trypanosomata, and their possible carriers, such as the "glossina morsitans" or tse-tse fly in sleeping sickness and trypanosome fever, and perhaps some kind of bed-bug or other biting insect (? Ornithodorus morbata) in relapsing fever (also called spirillar fever, billious typhoid by Hirsch, and famine fever by Murchison), a disease very ably studied by Vandyke Carter of Bombay, by Obermeier, by Lyell (Yusufzie valley, India, 1852-53), by Jamieson (Upper India), by Sir Robert Christison (notably in the case of Professor Hughes Bennett) and by Dutton. Koch, in his earlier researches into this disease, along with Carter, succeeded, as far back as nearly thirty years ago, in inoculating apes with the blood taken from a patient in the paroxysmal stage of the disease, producing an intense form of fever, and finally recovering the "spirilla" from the blood of those animals (vide British Medical Journal, 1877, p.700). Some form of bed-bug or biting insect,-(it has been suggested, the Ornithodoros savignyi, described by Neumann in his "Revision of the Ixodidae"),-is said to be similarly implicated in the spread of the Leishman-Donovan, Cachexial or Dum-dum fever and Kala-Azar or Febrile Tropical Splenomegaly, the name suggested by Manson. This authority, moreover, in an article describing two cases of this disease, (vide British Medical Journal, November 11th, 1905, p.1263), makes the suggestion that perhaps Oriental sore is etiologically the manifestation of a benign form of the same trouble as that which kala-azar represents in such a malignant manner. He bases this hypothesis on the observation of the morphological identity of the Leishman-Donovan body of kala-azar and the organism found in Oriental sore, and the assumption that they are also specifically identical germs. He suggests the possibility of Oriental sore bearing the same relation to kala-azar that vaccinia does to small-pox, remarking that inasmuch as Oriental sore occurs mostly in countries in which the camel is a prominent domestic animal (and victim to a form of trypanosomiasis known in India as "surra", due to the T.Evansi, discovered in 1880, and ascribed by the natives to the bite of certain of the Tabanidae or breeze-flies, a family of insects belonging to the order Diptera),-it is probably caught from the camel after the virulence of the germ has been got rid of by passage through that animal, just as the small-pox germ is deprived of its virulence by passage through the system of the cow. If this conjecture, which is worthy of being considered, should prove correct, he concludes we might have ready at hand a means of preventing the more formidable disease, kala-azar. In the smears we had the opportunity of making nearly two years ago, from a series of seven cases of Oriental sore under our care, as Medical Officer of the 5th Cavalry, at Dera Ismail Khan,- (the trouble being ordinarily spoken of there as "frontier sore"),- the characteristic protozoon was identified by Major S.P.James I.M.S. in all the specimens taken from cases recently admitted to hospital, as compared with those we had treated over a fortnight with carcompresses, and the results of this interesting investigation were noted on pages 5 and 6 of No.13 of the Scientific Memoirs (new series) for 1905, published under the authority of the Government of India. We might add that in our experience of a large number of cases of this affection, so rife on the North-West frontier of India, there was in every instance a history of the bite of some insect, generally said to be a mosquito. The native of Hindustan expressed the origin of his trouble in the words "Mucchur nay mujhko kata tha", and the Pathan by saying "Mashai may chechullay dai", meaning that a mosquito had bitten him.

There is perhaps no department of medical study in which, as we have said, such rapid and extensive progress has of late years been made as in that of tropical epidemiology in general, including tropical parasitology and the relation which the latter bears to the former. So intensely full of interest is the whole group of subjects that it is with much regret we leave it, or rather leave off here and for the present only, for it is a study that fascinates and enthrals to such an extent that it is not possible to sever connection with it but one must needs follow every advance made in it, with ever increasing interest and avidity.

And now, a word more ere we close this chapter. In science everything requires the support of incontestable proof, and it is this which is frequently most difficult to obtain. Analogy may supply the place of many a want, but proof is what we really need. The true scientific spirit does not allow the wish to become father to the thought, and thus it conforms to the maxim,-

"Sapiens nil affirmat quod non probat".

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## CHAPTER II.

### PLAGUE.

Its history, bacteriology and epidemiology.

The earliest accounts of plague such as we understand the term to mean at the present day, reach back, according to Hirsch, only as far as the third century of the pre-Christian era. It must be admitted that the material is very insufficient for illustrating the ancient history of the glandular plague and it may justly excite surprise that the historian Procopius, in the sixth century after Christ, should be the first writer to give anything like a complete description of the disease. Still there can be no doubt whatsoever that the trouble existed and was recognised long before this time, as the frequent mention of pestilential buboes by previous authors makes it clear. At all events, it was in this light that matters were viewed by the commentators on Hippocrates who lived after the glandular plague was properly described. Distinction must carefully be drawn between the term "plague" as used by the ancients and that employed at the present time. As Claudius Galen, commonly known as Galen, the celebrated physician who lived from 130 to 200 A.D, explains in his "Commentary on Hippocrates", by plague in the earliest times was meant an epidemic fever of a fatal nature, including epidemics of diseases other than that to which we at present limit the application of the term, for instance such maladies as are marked by prominent choleraic and dysenteric symptoms and have a tendency to spread amongst many people. On consulting the history of the Peloponnesian War which opens the second Book of Thucydides, a very graphic description is found of what is known as the "Plague of Athens" which raged in the year 430 B.C., an outbreak sometimes called the "Plague of Thucydides", since that Athenian historian was affected with the condition and was one of the few who recovered. In describing the symptoms of the disease in the seventh chapter of his Second Book, he says "this I can the better do as I had the disease myself and watched its operation in the case of others". The opinion that this epidemic disease was of the nature of a severe bowel-complaint in which dysentery played an important part, is justified by the description he subsequently gives of it. That the opinions of authorities as to the true nature of the disease constituting the great plague of Athens differ very considerably, is quite manifest, and Dr Charles Collier, writing in 1857, refers to it as an outbreak of the nature of a malignant scarlatina. Thucydides leaves a celebrated account of the bubonic form of plague, its symptoms, duration and sequelae, holding that the disease never attacks the same person more than once, an opinion in which he is supported by later authorities like Massarius, Diomedes Amicus, Sir William Pym and others, but not by general experience. A.Cornelius Celsus, a Roman physician, who lived during the times of the Emperors Augustus and Tiberius, that is about the time when Christ was born, in the account of plague embodied in his great work "De Medicina" written in eight volumes, deals with the disease more from the point of view of management and prevention than with regard to its symptoms. The historians Appian, Lucian, Pliny and Plutarch make reference to the disease in their works. Galen unfortunately gives no proper description of the dreadful plague that prevailed in his time, for it appears that he fled from Rome for fear of the infection; he alludes to it indeed in several parts of his works, but only in very brief terms. Another ancient writer on the subject is Aetius, a Greek physician of the end of the fifth or beginning of the sixth century, who made a compilation in sixteen volumes from many authors whose works have since been lost. Still others are Oribasius, Paulus Aegineta, Nonnus, Psellus ("Opus Medicum"), Actuarius (Meth.Med. ii) and Ruffus of Ephesus, a physician who was a contemporary of the Emperor Trajan (98 to 117 A.D.) and by whom, according to M.Littré, buboes are noticed among the symptoms of plague (Littré's "Hippocrates", ii, p.585). The first great extension of the disease in Europe occurred in the sixth century of the Christian era and was known as the "Plague of Justinian". It commenced at Constantinople in 543 A.D., in the fifth year of the reign of Justinian, and, lasting about fifty-two years-, wrought fearful devastation wherever it appeared. Evagrius (or Evagrius), in his account of this epidemic which, he says, both resembled and differed from the plague of Athens in many respects, relates that during these times many persons who recovered from the first attack, sank under a second, and his view as to the possibility of the occurrence of a second attack is upheld by the opinions of Ficinus, Joubertus and many later authorities, and corresponds to the reports of the Parel Hospital, Bombay, which state that "one attack does not confer immunity from another". To Procopius, the classical historian of the great outbreak which desolated the Roman Empire in the reign of the Emperor Justinian and outlived the writer of its history, is due the credit, as stated before, of recording the first full account of this disease. The malady resembled the plague of Avignon which lasted from six to eight weeks and was described by Guy, of Cauliac. Agathias describes the plague of Justinian on its second return to Constantinople in 558 A.D. and compares many of its features with those that characterised the plague of Athens. Amongst the most prominent Arabian authorities of early times to describe plague are Avicenna, the physician who lived from 980 to 1037 A.D., and Rhases.

The history of plague from the days of Justinian is very deficient until, coming down to more recent times, we reach the period of the next great outbreak, in the fourteenth century, known as the "Black Death", the most terrible calamity of its kind that has befallen our race. Guido is cited by Dr Freind as authority for the opinion that the Black Death had its origin in India. It spread over the whole of the then known world, even to far away Greenland, and destroyed from a quarter to a half of the population of Europe, or, according to M. Hecker, about 25 millions of human beings. Following this there came another long period of quiescence or freedom from the disease in epidemic form, for during that time plague still remained endemic in England and Western Europe generally. In the middle of the seventeenth century it burst out again and the last great outbreak in England was the famous "Plague of London" of 1665, which claimed no less than 70,000 victims. In France the last epidemic occurred at Marseilles in 1720, spreading thence through Provence.

Such is a very brief sketch indeed of the history of this disease as it occurred in ancient times and in the middle ages, in Europe generally, not including the Balkan peninsula and the south-eastern portion of the continent, for in these places numerous outbreaks of greater or less magnitude have made their appearance from time to time, as also in countries further east. It is with this short account of the epidemiological history of plague that we have thought fit to open this chapter, and now, ere we pass on to considerations still more directly concerned with the special nature of our work, it only remains that we should briefly discuss the nomenclature of this disease and make ourselves clear regarding one or two points connected therewith. Dismissing at once as unscientific such terms as "black death", we come to the name "bubonic plague" which of all others has been the one most popularly employed to denote the disease. The term is distinctly unsatisfactory as it can only apply to a form which, though probably the commonest, is still merely a single one of the several forms of the declared disease, known as bubonic, pneumonic, septicaemic, abdominal cutaneous. It is preferable by far to reserve the term "bubonic" for that form in which buboes constitute a prominent and leading feature of the disorder, and to apply the unqualified term "plague" to the disease in general, the "morbus pestis" of Cullen, a specific, infectious and highly contagious affection, inoculable on certain animals and characterised by the following peculiarities in its epidemiology, namely, (1) long periods of quiescence, (2) extraordinary extent of range, (3) rapidity of diffusion, and (4) want of amenability to treatment.

The disease has been variously defined by different authors. The definition offered by Dr Brown is "an exanthematous disease, the eruption consisting of buboes, carbuncles and pustules, white, livid or black, and generally attended with malignant and very fatal fever"(Cyc. Prac. Med., Art.-Plague). At the present time the essential feature of the trouble is recognised as being of the nature of a septicaemia, associated with a local inflammatory process. The latter is well marked in the various clinical types of the declared disease, except in what is known as the "pestis septicaemica" where it is not sufficiently pronounced to attract the attention of the clinician and where the general septicaemic element proves very rapidly fatal.

With regard to the contagious nature of the disease, although well known to us in modern times as an intensely marked feature, it was not even suspected by the earlier ancient authors as entering into the etiology of this febrile malady. Thus, Homer refers the origin of the plague that prevailed in the Grecian army during the siege of Troy, to the heat of the sun. The works of the fathers of History and of Medicine may be ransacked in vain for any traces of allusion to the doctrine of contagion. If the Mosaic description of leprosy be excepted, the first positive reference to the contagious nature of diseases is to be met with in the works of Thucydides, for his description of the plague of Athens, previously mentioned, leaves no doubt that he wished it to be understood that the disease was transmitted from person to person, as physicians owing to their greater intercourse with the sick, were more attacked than others, and as citizens were constantly seized with terror at the approach of those labouring under the disease, for it was often contracted by such intercourse. Ovid (Metam. v,551) gives poetical form to this idea, as also do Lucretius and Silius Italicus. The historian Procopius was a non-contagionist. The philosopher Aristotle raises the question of the contagiousness of the disease (Probl.i), and the elder Pliny (Hist. Nat. xxxiii,80) mentions the contagion of the pestilence, as also do Marcus Antoninus, the philosopher,- Chrysostom (In Joan. Orat. lvii), Seneca (De Tranquil. vii) and Isodorus Hispalensis, a much later writer, whose language is very precise when he says "Pestilentia est contagium quod quum unum apprehenderit celeriter ad plures transit". Aretaeus, a Cappadocian and eminent physician, who flourished during the reign of Vespasian (70 to 79 A.D.), in the course of his eight volumes on diseases in general, appears to be the first author to allude to contagion in unequivocal terms. Caelius Aurelianus, who was nearly contemporary with him, mentions plague as a contagious disease, while the various Latin medical authors like Oribasius, Alexander, Synesius, Palladius and Actuarius omit all allusion to this point. Among the Arabians, Rhases mentions plague as a disease which is "transmitted from one person to another". Avicenna and Haly Abbas include plague in their list of contagious diseases, the former calling small-pox and measles the most contagious of all maladies; while Avenzoar, in his works, alludes to the matter of contagion. Thus all or, at any rate, the most intelligent of the ancient medical authorities, while holding that fevers of a mild nature with no tendency to putrescence, are not communicable from one person to another, maintain that plague is so communicated in consequence of the atmosphere around being contaminated with putrid effluvia, though not by means of any specific virus. Galen frequently mentions a poison being found in the human body, but does not refer to any specific virus transmissible from person to person, though he does allude to the animal fluids becoming so altered as to be deleterious. Even within more recent times than we have so far dealt with, the matter of the contagiousness of this trouble has been made the subject of much discussion. Tweedie, in his article on this disease (System of Practical Medicine, i) goes very fully into the question and recounts both the reasons that have been advanced in favour of plague being a contagious disease, as well as the chief objections put forward by the anti-contagionists against such views. He says that "the statements of each party are sufficiently contrary; it may therefore be supposed to be somewhat difficult to arrive at any decided opinion on the question", and, writing of his own times and with regard to his own beliefs on the subject, he makes the statement that the "communication of plague by inoculation with the matter from a bubo or with any other morbid product, has by no means been proved; on the contrary there is every reason to believe that the disease cannot be produced by these means". On this very point Manson remarks, -"the pus from a bubo is not always infective. Inoculation made with such may fail. Apparently the bacteria of suppuration may kill the bacillus pestis", -a statement made in the light of our present knowledge. We shall have occasion to deal further with this subject when we come to consider the channels by which the virus is discharged from the body, the vehicles by which it is conveyed into the system and the channels of infection or ports of entrance, with reference to plague.

Before we made this departure into the question of the contagious nature of plague, we had traced the occurrence of the disease in epidemic form down to the latter part of the seventeenth century. During the following two centuries the disease in Europe withdrew eastwards and at the end of that time was confined almost exclusively to parts of Turkey and Southern Russia. In 1894 an epidemic commenced in Hong Kong during which, within three months, 2,500 people succumbed. This outbreak aroused fresh interest in the study of the disease and the researches that were carried out, resulted in the discovery in that year, independently by Kitasato and by Yersin, of the specific causative organism, the bacillus pestis. This important and epoch-marking discovery has, as might well be imagined, revolutionised many an idea that had hitherto prevailed on the subject of this disease, its causation, mode of spread, etc. Within the comparatively short period of twelve years since that time, much advance has been made in our knowledge of the bacteriology of plague, and, <u>pari passu</u> with this, much progress in that regarding its epidemiology. We shall now proceed to consider the former and trace the practical bearing it has on the latter, in short, study the relationship which, so far as we know at present, the bacteriology of plague bears to its epidemiology.

Let us then commence by reminding ourselves of the characters of the plague bacillus. Morphologically, it is a short, thick cocco-bacillus with rounded ends, having, according to Gordon, a single terminal flagellum and a capsule or, at any rate, the appearance of one, especially in the case of the bacillus present in the blood. Most observers, however, regard the organism as non-flagellated and as having no true capsule but only a finely granular, faintly stained envelope around it, consisting of a kind of gelatinous substance binding individuals together. The organism is said to be dumb-bell shaped in the blood of infected animals, cylindrical in the spleen and lymph glands, and occurring in chains of rods in the peritoneal fluid. According to Kitasato, the bacillus is non-sporebearing.

With regard to its staining characters, the organism readily responds to the action of the various anilin dyes, the ends staining deeper than the interpolar part, (the so-called "polar staining"). Gram's method gives a negative result with this bacillus.

As to its cultural characters, the organism, like others that are pathogenic, grows best at blood-heat, $36^{o}$ to $39^{o}C$. On slope jelly the growth somewhat resembles that of the diphtheria bacillus, forming a gradually thickening, whitish band with irregular and knobbed margins and giving rise to no liquefaction. In a stab jelly preparation, the line of inoculation develops closely packed, round, dust-like colonies, brownish in transmitted and white in reflected light, with no liquefaction of the medium. In bouillon, after 24 to 48 hours, the medium becomes rather turbid, but after a day or two longer the granules and flocculi become deposited at the bottom of the tube, leaving the supernatant fluid clear; an imperfect, whitish, easily broken pellicle forms on the surface in a characteristic manner, and a broth which contains an alkaline litmus-blue solution, becomes red in the course of a month or so. On agar or, better still, glycerine-agar, the growth shows a greyish-white, slimy, viscid, translucent, linear appearance which rapidly spreads into a band with crenated, knobbed edges. In milk, the growth does not cause a curdling unless kept for a month or so. In plate gelatine, the organism grows well at a lower temperature than that of the blood and produces, in twenty-four hours, colonies that are as a rule grey and punctiform, translucent and angular, though sometimes atypical and filamentous in the early stages of their growth; in three to seven days such colonies become greyish-white, more or less rounded, thicker in the centre and presenting a moist surface. The colonies lying below the surface of the jelly are small and spherical, brownish in transmitted light and white, sometimes with iridescent borders, in reflected light. While the organism, as has been stated, develops best at blood-heat, it is killed by thorough drying, as well as by exposure to a temperature of 60°C. for five minutes, with certainty in a broth culture, but not so certainly if the growth be on jelly because the bacilli in the depths of the medium are not always exposed to the same degree of heat. But a temperature of 62°to 65°C. for ten minutes will kill the bacilli under any of these circumstances. The virulence of the bacillus is susceptible of modification, for it is capable of being both intensified and attenuated, by either natural or artificial means. Rapid growth of a culture decreases its virulence, and prolonged growth on artificial media does likewise. Direct sunlight is inimical to the germ, killing it in five hours or so, whereas in the absence of sunlight and fresh air, and in the presence of $CO_2$ the organism tends to flourish. In water the infective power is said soon to be lost.

So far we have considered some of the morphological, cultural and other characters as originally discovered and subsequently studied by most workers on the subject. But Klein, who has recently carried out a series of researches on the bacteriology of this disease, expressed in 1904 the view which he repeated in the following year, that two strains of the bacillus pestis were to be distinguished, namely, (1) the virulent "human" type, and (2) the less virulent "rat" type. These, he maintains, differ from one another in form as well as in cultural and physiological characters, and the differences are of a definite and permanent kind. According to him, the bacilli of the human type are of a more or less cylindrical shape; in gelatine cultures the growth of the colonies is, at an early stage, conspicuously granular and somewhat opaque in appearance; the bacilli are very virulent for the human species, and cultures of the organism are highly so for rodents. The bacilli of the rat type, which have presumably passed through several generations in the rat, are less cylindrical than those of the human type; they exhibit oval and coccus-like forms and show a tendency to undergo involution rapidly; their growth on gelatine is, in early phases, of remarkable translucency and the colonies are less angular than those of the human type; their action on the guinea-pig (and presumably on man) is less virulent and, by transmission in artificial cultures, the virulence is soon lost. Klein does not think that the rat type is due merely to an attenuation of the more virulent organism by continued residence on artificial culture media, because the human type retains a considerable degree of potency through many generations of sub-cultures for several years, whereas the rat type quickly loses its virulence almost completely. Moreover, the former type rapidly recovers its full powers by a renewed passage through the animal body, whilst the original virulence of the latter (rat) type, when once lost by artificial culture, cannot be regained by animal passage. Klein recognises that these two types of bacilli have in all probability descended from a common stock. He has not, however, succeeded in converting the rat type into the human type, though he has met with more success in his efforts to modify the latter into the former type. For this purpose he has employed passage through rats previously protected by subcutaneous inoculation with Haffkine's prophylactic. Klein's observations are similar to those made by the German professor, Kossel, regarding the differentiation of the bacillus of tuberculosis into the human and animal types, as previously pointed out. They are worthy of consideration in that, when further developed and finally decided, they are likely to throw much light on the nature of the organism and its habits, as well as on the connection of the disease as it occurs in man and in the lower animals. Be this as it may, we are at the present time, and have been for the past few years, certain, thanks to advances in bacteriology, that there does exist a very definite connection, amounting to a specific relationship between the germ discovered by Kitasato and by Yersin in 1894, and the disease, plague. Nor can there be the slightest doubt regarding the specific nature of the bacillus pestis, inasmuch as it satisfies fully all the requirements laid down by Koch in his postulates.

With regard to its habitat in the body, the organism has been found to occur in the buboes, generally in pure culture, though in the later stages it is often associated with pyogenic cocci; in the spleen, lungs, intestines, kidneys, liver and other viscera; in advanced septicaemic cases it is found in the blood where it becomes more abundant towards the end of rapidly fatal cases; it is also present in the sputum in the pneumonic variety of the disease. The difference in morphology of the germ as found in the spleen, lymphatic glands, blood and other fluids of the body respectively, have already been noticed briefly. The simplest practical method of examining the blood of a patient for plague bacilli and one that we have found invariably to give the best results in a great number of cases, is the following. A large drop of blood is taken from the patient's finger, the skin surface over which has previously been thoroughly purified; the blood is spread out on a slide by means of a needle so as to form a smear which is subsequently dried in air and fixed by passing carefully over the flame of a spirit lamp or a Bunsen's burner; the slide is then laid out flat at the bottom of a dish containing distilled water, in order that the haemoglobin may dissolve out and the smear be completely decolourised; this is then gently dried over a flame, stained with methylene blue or carbol fuchsin, and examined under the microscope.

Such is a resumé of the main facts comprised in our knowledge as it stands at the present time regarding the pure bacteriology of plague, and we next proceed to consider some of the epidemiological features of the disease in the light of what we know regarding the germ specifically implicated in its causation.

To begin with, the nature of plague is such that, although it breaks out from time to time in epidemic form, generally at long intervals, yet it constantly or, at any rate, frequently exists in certain localities, like a smouldering volcano, ready to burst out under suitable conditions, and to devastate everything that comes within the range of its action. Such localities as constantly harbour the disease, or "endemic centres" of the disease, are at the present day to be found, going from east to west, (1) in the mountain valleys of Yun-nan, in China, on the eastern borders of Upper Burma, a locality which appears to have been the starting point of the present great pandemic; (2) in parts of Mongolia, north of China; (3) in the Kumaon and Garhwal districts in India, on the southern slopes of the Himalayas, at an elevation of 4000 to 7000 feet, on a latitude between 28° 14′ 15″ N. and 31° 5′ 30″ N., and on a longitude of 76° 6′ 30″ E to 80° 58′ 15″ E.; (4) in parts of Mesopotamia, especially Baghdad, and the neighbouring hilly provinces of Persia; (5) in Assir, a mountainous district of Arabia, corresponding roughly to the 20th degree of northern latitude and the 43rd degree of eastern longitude; (6) in the province of Tripoli, an elevated plateau on the southern shores of the Mediterranean Sea, a locality which is believed to have kept Egypt supplied with the infection in the days of the ancient Egyptian epidemics; and (7) in parts of Africa, especially about the Uganda region of Central Africa, at a height of some 5000 feet. Evagrius, in his account of the plague of Justinian, mentions that the disease was supposed to have originated in Ethiopia (corresponding more or less with the parts we have referred to, around the upper reaches of the Nile) and from thence to have spread to Egypt, Lybia and to the Persian Empire.

Considering these facts, two points at once suggest themselves to one's mind, first that the birthplace of the disease appears to be the sub-tropical regions of the East, and secondly, that inasmuch as plague is always or, at any rate, generally to be found present in localities such as those mentioned, there must be certain characters peculiar to those centres, possessed by them in common and associated with the endemic existence of the disease and probably also connected with its epidemic spread from time to time. On enquiry into the subject we find that there are many and marked features which characterise all these places and which are related to plague in a very definite manner. For instance, all such localities swarm with rodents, contain overcrowded, ill ventilated, dirty houses in which cattle generally find shelter along with or in very close proximity to man, and where there exists a system of imperfect burial of the dead close to or around human habitations. These few lines contain the leading facts regarding such places, embodied in the many excellent descriptions given of endemic plague centres by various commissions of enquiry. For example, in such an account of a centre in Tripoli, attention has been drawn to the low doorways of the houses, the small windows opening or to filth-covered courtyards, and the presence of a graveyard in the middle of the village, near a pool of stagnant water, while it was also shown that the dead were disposed of in shallow graves from which they were subsequently unearthed by jackals at night and strewed about the place. Similarly, a British Commission, reporting on an endemic centre in the Himalayan regions referred to, describes the low-roofed houses which accommodated both man and cattle and were surrounded with dung-heaps, while the overcrowding, want of ventilation and presence of bad smells could not escape the notice of the most casual observer. Cutch Mandvi, now well-nigh rendered famous by the graphic and classical description of it given by the Indian Plague Commissioners in their Report, is an admirable example or type of the numberless places of a like kind to be seen all over India even at the present day. The town of Cutch Mandvi has suffered terribly in the course of this epidemic. It is a sea-port, with a population of about 38,000, is roughly a square mile in area and is surrounded by a wall twenty feet high containing several gateways. For an excellent account of the inhabitants and their habits, of the construction of the town, its thoroughfares, drainage and conservancy systems, or rather the absence of these, of the methods of disposal of the dead and other particulars, we refer our readers to the report we have mentioned. As regards the imperfect burial of the dead, it is not known exactly in what manner this favours the endemicity of plague. Creighton, the celebrated epidemiologist, in referring to the point, says that the clergy for instance suffer comparatively greatly as they are more in the way of being associated with the products of cadaveric putrefaction.

Now, in passing on to the epidemiology of plague and the relation which the bacteriology of the disease bears to it, we will adopt the plan of taking up a series of points in connection with the subject, discussing each separately, and endeavouring to make the dissertation as complete as possible for a short work of this nature.

I. Sources of the virus.

These comprise:-

(1) Rats and other animals.

(2) Man.

(3) Growths in other media.

The first of these points involves the recently much debated questions of plague as a disease of the lower animals, the identity of the malady as it occurs in these creatures and in man, as well as two points which we shall take up later on, namely the agency by which the disease is transmitted from rat to man, and the manner in which the carriers impart the infection to man. Plague differs from other epidemic maladies in that a vast number of lower animals are susceptible to it. Professor W.J. Simpson, late Medical Officer of

Health for Calcutta, on a special expedition which he made to Hong Kong for the purpose of investigating the subject, found as the result of his work that not only rats, mice and rodents generally, but also monkeys, cows, sheep, pigs, cats, fowls, turkeys and ducks were all susceptible to, and able to harbour, the trouble. Of these creatures some are domestic, while others are not, and the usual way in which, according to him, they derive the infection is by eating contaminated matter. Moreover, the disease occurs in the fleas which infest these animals, judging from the discovery of its specific germ in the interior of these insects,-a discovery that carries us a stage further than the times when Hunter, referring to the distribution of the disease generally among the lower animals, wrote "Practically every vertebrate animal found in the immediate neighbourhood of man, may be rendered plague-infected". There is little doubt at present, however, that of all animals, rodents are the most susceptible; in fact, as Davidson points out, "plague is probably primarily a disease of rodents", and further, that "there is good reason to believe that the tarbagan plague <u>originates</u> in these rodents". Clemow has shown that the tarbagan (Arctomys bobac) is one of the marmots, a genus belonging to the order Rodentia or Glires, and that it lives in Mongolia, burrowing in winter and, during the long droughts of summer, that is from March to September, living on the bare plains. These animals are hunted for their skin and at such times they probably hand on to man the disease which they are said to originate; thus the plague spreads to villages. The animal is said also to inhabit parts of the Himalayas. So far as man goes, however, the first source of the virus is the rat and, according to many authors and to the experience of numerous epidemics, most outbreaks are heralded by an increased mortality amongst rats. The manner in which they are said to diffuse the disease will be seen later on when we come to consider the modes of transport of the virus. With reference to some of the opinions of ancient writers on these matters, it might be mentioned that Virgil (Ecl. i, Georg. iii, 464) alludes to the infectious nature of certain diseases in cattle, while many of the old writers on veterinary surgery and agriculture, in like manner, say that the plague of cattle is infectious. As to the rôle played by rats in the spread of the trouble, it has been held that the infection of these animals, though often associated with outbreaks in man, is not invariably so, as is shown by the experience of other places besides India, where plague has been epidemic. In many epidemics of earlier times there is little mention of the circumstance. Dr Rudolf Abel, in a valuable paper on this subject, gives the result of much painstaking research and, commenting on the want of reference of rats in relation to the plague epidemics of Europe since 1730, he suggests that improved sanitation is probably the reason why Europe has since that date been less liable to outbreaks of plague. In the first recorded plague epidemic in the Bible there is no causal relationship actually described between mice and plague, but it would appear that while the Ark, which was captured by the Philistines and taken to Azotus, remained there, the people of that city suffered from "emerods" and at the same time there was a great mortality in the city and an invasion of mice (or rats) in the villages and fields. Avicenna (980 to 1037 A.D.) makes the first distinct allusion to the subject, but it has been suggested that his writings refer to Asiatic, chiefly Persian, epidemics. In an ancient "Purana", dating back more than 800 years, it is written, "When you notice an unusual mortality amongst rats, it is a sure sign that you are to be shortly visited by a fatal disease, and your only safety lies in flight",-a piece of advice given to the Hindus many years ago and one which, besides still holding good amongst them, shows us that the people, even in those ancient times, had realised the relationship that rats bore to this epidemic disease. In the Constantinople outbreak of 1348 and in one at Moscow in 1771, the association between the death of rats and the occurrence of plague, appears to have been observed quite well. Coming down to our own times, we find that at Jeddah, in 1898, there occurred a small outbreak while many infected rats were seen crawling about the place; the trouble did not at that time spread very far, but in the following year it returned on a larger scale and, after it had ceased, a high plague mortality continued among the rats and mice for a while. In the Oporto epidemic, in 1899, although cases of direct infection did occur, there was no epizootic reported to exist amongst rats. In the first outbreak at Glasgow, in 1899, no infected rats were reported, but in a subsequent epidemic, a year or two later, numbers of dead rats were found at the Central Hotel in that city and these were traced to have come viâ subways and tunnels from the dockyards; the bodies of these animals were examined bacteriologically and found to contain the bacillus pestis. The Sydney epidemic differed from the first outbreak at Glasgow in that (a) cases of infection by contact with plague patients were rare, and (b) plague occurred as an epizootic among rats which it was said not to have done at Glasgow in the first instance. In 1904 Sydney was visited for the fourth time with an epidemic of plague which happily was limited in extent. Dr Ashburton Thompson, Chief Medical Officer to the New South Wales Government, in a report on this outbreak made for the Board of Health, enters into a discussion on the etiology of the disease based on its observed epidemiology. His studies demonstrate that an epizootic disease, plague, among rats preceded the first local case which occurred in man and that the area over which the epizootic extended was practically co-extensive with that on which cases of plague in man were observed. As the epizootic died out the epidemic ceased, the cases in man evidently being communicated by infection from rats. Perhaps Thompson is right in not committing himself by any definite opinion as to how this communication takes place as, for example, to the flea hypothesis, for in view of some uncertainty still prevailing on the mode of transmission of the disease from infected rats, further experiments with fleas conducted on a scientific basis, are urgently needed. Tidswell found many fleas on rats even during the second (1902) epidemic in Sydney, but when the epidemic was over, he could find but few. This subject will be taken up again later, in considering the channels of infection. Meanwhile, restricting ourselves to the question of rats as a source of the virus, it is interesting to note the views of the Indian Plague Commissioners regarding it. In enumerating the causes of the spread of plague from infected localities, they give the first place to human agency, including in this infected articles of clothing and merchandise carried by man, and next they make mention of rats. In fact, they are a little sceptical in the matter of attaching the importance which others do to the connection between the rat and man in plague incidence and plague epidemics, as may be seen from the opinions embodied in the following remarks made by them,- (1) in some places where several epidemics have occurred among men, rats have not been infected at all, and in many places where there have been plague epidemics among men, the disease has not appeared among rats in epidemic form; (2) occasionally there has been a considerable mortality among rats and no plague among men; (3) even when there has been the largest amount of plague among rats, the risk to persons coming in contact with them appears to have been less than that due to inhabiting houses in which there were plague patients, or to coming in contact with pneumonic plague; sometimes, however, a large number of plague cases in a village have been directly attributable to an epidemic among rats; (4) a severe epidemic among rats must tend to the spread of infection; and (5) when plague is once established, there is no doubt that human agency is a more important factor than rats in spreading the disease. At the present day, however, it is perhaps universally held that rats constitute the first source of the virus for human infection and that man comes by a long way second. Much testimony has of late years come to hand regarding this important relationship between rats and man in the matter of the diffusion of this epidemic disorder, as we shall have occasion to observe when dealing with the question of prevention. As to the particular species of rat on which this serious responsibility is thrown, it is the ordinary black rat (Mus rattus) an inhabitant of houses, as differing from the brown or grey rat, or Norway rat as it is sometimes called, (Mus decumanus), an inhabitant of sewers and underground passages and therefore having less contact with man. The former is known to be the indigenous species of the plague endemic areas, and its disappearance from England and from Western Europe generally in the seventeenth century or, at any rate, the fact that it has become a very subordinate occupant of those parts since that time, has been associated in a causal manner with the co-incident disappearance of plague from that area. While on the subject, it might be as well to refer to the opinion of the Indian Plague Commissioners on the mode in which the rats themselves derive the infection. The Commissioners believe that the alimentary canal is not the common route of infection, but they consider that the data available from the post-mortem examination of rats do not allow of a final verdict as to whether these animals in a state of nature are generally infected viâ the skin; they think that the nasal mucous membrane is, of all channels of infection, the most likely one in such cases, as for instance where outbreaks of the trouble among rats are traceable to importation of infected clothing and articles of a similar nature.

With reference to the same matter of rats and plague, Bruce Skinner, in a series of well written papers which he has contributed on the subject, starting on the assumption that these animals do not originate the disease, endeavours by a study of the habits of these rodents in relation to the seasons of the year and to the seasonal incidence of plague, to establish the actual manner in which blame has come to be attached to them, and the extent to which they really merit such blame. If these creatures do not initiate the trouble (and animals cannot be said to initiate any specific fever), then they themselves must contract it from some extraneous source, and the question comes to be, which is the source? The study of such a subject in a country like India, with its vast extent and climatic changes neither equal nor synchronous in different localities, comes to be a matter of exceedingly great difficulty. Still it is observable generally that in dry weather rats live out of doors, whereas, with the advent of the monsoons and the heavy rains, they betake themselves to shelter indoors. This applies to most parts south of the Punjab, for in that province the rains being comparatively less copious and the winter severe, the habits of these animals are probably reversed. The point is now that plague in India, as was formerly the case with the great epidemics of this disease in Europe, being most severe while the rats are out in the fields, Skinner suggests that though these animals suffer from plague, they are not the source of the disease; for, he argues, that were they the source, the epidemics would be most acute when the rat is in most intimate contact with human beings, and, moreover, he says, there is nothing to show that the destruction of rats reduces plague incidence. Further, he adds, that our energies are entirely misdirected in trying to exterminate these creatures for "inasmuch as it (the source of the virus) must be something outside the rat, it would appear more scientific to adapt our defensive measures to our immediate surroundings rather than to destroy those animals whose misfortune it is to suffer in common with ourselves from pestilence", especially as "rats in towns are valuable scavengers". This writer is, needless to say, not by any means a believer in the flea-convection theory. His idea is that rats and man derive the infection at the same time from some common source, that is when both are out in the fields together. To discover the nature of this source he makes a study of the various forms of cattle disease, including rinderpest or steppe-murrain; foot and mouth disease; quarter-ill or charbon symptomatique; pleuro-pneumonia; anthrax; ghotwa, ghotu or galghotu, a condition first reported as a distinct disease by W. Pease, in 1896, corresponding to the "buffelseuche" in Hungary and resembling glos-anthrax; and finally, an epizootic referred to by Yersin as occurring in the

Chinese province of Tonkin and called "peste bovine". The suggestion he makes is that the disease is carried to man, as it is to rats, from cattle affected with similar trouble, the probable carrier being some biting insect like the "Hyalomma aegyptium", one of the Acaridae. He bases this suggestion on a knowledge of the distribution of the tick which, normally inhabiting endemic plague areas and extending its borders during favourable years, would satisfactorily account for the extension of plague during periods conducive to its existence in a new locality. These Ixodes lay their eggs or produce their young in the earth and, when hatched, these attack their future hosts, dropping off only when the period of delivery of the female is at hand. He endeavours to explain the seasonal abeyance of plague in winter in countries like Russia, and during the rains in places such as Lower India, by saying that under the former conditions the young hibernate in the soil, while under the latter they generally get washed away from its surface. Similarly, the carriage of plague in ships, usually attributed to the pest bacillus in the cargo finding an inoculable spot in the victim, is explained by this writer by saying that the eggs of a plague-infected species of the Ixodidae are present in cargoes, the larvae at birth finding occasional hosts on the voyage or when the cargo is unloaded. Further, he says that the importation will result in an epidemic or not, according as the country where the cargo is discharged possesses climatic and perhaps telluric conditions favouring the invasion of the particular species of tick concerned. This is analogous to, and reminds one of, the case of yellow fever and its convection by mosquitoes of the genus culex, known as the Stegomyia fasciata. Besides the possibility of the tick being the medium for conveying the disease from animal to man, he states that it may act by carrying it from the soil to both man and animal. The studies carried out and the observations made by Bruce Skinner, though resulting in conclusions not in keeping with the generally accepted views regarding the part played by rats in the spread of plague, are still worthy of consideration as representing the outcome of work carried out on a scientific basis and suggesting possibilities from a fresh point of view on a subject not yet fully cleared up. In favour of the assertion of Skinner that the rat is not a source of the virus for man but a victim to the scourge in common with man, is the fact that in several old-time epidemics of plague the outbreak was not found, or, at any rate, not reported to have been associated with an increased illness or mortality amongst rats, suggesting that possibly the latter circumstance is not essential for the occurrence of the former, or, at all events, that the rat is perhaps not the important source of the virus which at present it is generally held to be.

The whole subject wants further study and much elucidation, and, considering the zeal being shown in research work at the present time, and the plentiful opportunities being afforded by the existing epidemic of plague, the prospects are fair with regard to these points being speedily cleared up. The literature on this subject, namely, of the connection which rats have with outbreaks of plague, has of late reached vast proportions and many of the contributions to it are full of interest as containing the results of very useful experimental work carried out in a thoroughly sound and scientific manner. We shall return anon to the subject of rats and plague, but ere we leave it at all we would like to point out the special value which writings on such matters have when they contain the results of systematic and reliable experimental research. Dr Richardson, speaking in March 1858, on the "Investigation of epidemics by experiment", draws attention to the weakness of any system of epidemiological study which is not based on the experimental method and of course strongly advocates the wider adoption of the latter. In this connection, we would also refer the seeker after truth in matters epidemiological, to W. Budd, of Clifton's admirable memorandum on a scheme for the investigation of epidemics and epizootics, under seventeen headings, drawn up at the request of a Committee appointed for that object at the annual meeting of the British Medical Association, as far back as August 1862; and to E.Headlam Greenhow's paper "On the study of epidemic disease, as illustrated by the pestilences of London", read before the Epidemiological Society of London, at the opening of the session 1857-58, in which paper, it may be mentioned, he expresses his belief in constitutional predisposition existing amongst communities to enable the germs of disease to exert their morbific power, and he calls attention to the influence of meteorological phenomena in connection with the outbreak of epidemics; and finally to Dr Stokes's excellent introductory lecture on "The study of epidemics" delivered in 1862, at the Meath Hospital and County of Dublin Infirmary.

II. Channels by which the virus is discharged from the body.

Supposing the virus, derived from one or other of the sources we have just been discussing, has effected an entrance into the system of a victim, the question we have now to consider is, by what channels may it again be discharged from the body? The ways by which it may find exit from its temporary habitat are :-

(1) the buboes.

(2) the skin (pustules, boils, carbuncles, petechiae).

(3) mucous membranes and their secretions, (nasal secretions, saliva, sputum, faeces, urine).

(4) the dead body.

With regard to the virus finding a way out viâ the buboes, we have already quoted the views of Tweedie and of Manson, the former holding that it had not yet been proved that inoculation with the matter from a bubo or with any other morbid product was capable of communicating plague, the latter maintaining that the pus from a bubo was not always infective and that inoculation made with such may fail, as apparently the bacteria of suppuration may kill the bacillus pestis. That the buboes do contain the specific organism cannot of course be doubted for this indeed has been frequently demonstrated by bacteriological methods. Now in the bubonic form of the disease the bacilli are for a time completely sealed up or shut off from the surface of the body and from the outer world, but when the buboes are opened the infective material contained in them is discharged directly from the surface of the body, while if septicaemic symptoms supervene, the virus also finds an escape in the discharges from nasal, conjunctival, bronchial and alimentary mucous surfaces. This period of infectivity lasts from a few hours to a few days. It is difficult, owing to a want of data, to fix the length of time for which the bacilli are present in the pus from a suppurating bubo. If the latter is left unopened for a long time, the plague bacilli in it undergo degenerative changes to some extent and may even be found associated with the presence of pyogenic cocci.

Through the skin the virus may find exit when vesicles, boils, pustules or carbuncles are present. In the case of petechiae under the skin, as in the septicaemic form of plague, the organisms are said to be able to make their way out through the unbroken surface. Drs Calmette and Salimberi have remarked on lesions of the skin in plague. They say there is a particular form of the pest, recognised as far back as the middle ages and also by the German and Austrian savants at Bombay, in which the primitive lesion is represented by one or more pustules on the surface of the body. The pustule begins as a vesicle surrounded by a zone of inflammation, sometimes black, with sero-sanguinolent contents and filled with free pest bacilli. Certain cases reported by Captain Childe I.M.S. may perhaps belong to the same category, although such eruptions have not been frequently observed in Indian epidemics of plague.

Again, the nasal and buccal secretions have been found to contain the specific bacilli, especially in what is known as the cervical form of the disease, that is, where the glands of the neck are chiefly affected.

In the pneumonic variety the sputum contains the organism in almost pure culture during the whole course of the disease, having in one (primary pneumonic) case been recovered as many as thirty-three days after the return of the patient's temperature to normal. It might, in passing, be said that this has a very important bearing on the subject of isolation during convalescence, and it is the opinion of the authority, Sir Thomas Fraser, that as the bacteriological evidence supports the belief that a convalescent patient may cause infection even four to six weeks after all acute symptoms have disappeared, isolation should be carried out, in cases with pneumonic symptoms, for at least four weeks after the temperature has returned to normal. Russel advocates isolation until such time as certainty can be established and says that all convalescents should be kept under the ban of suspicion as long as any symptoms of the disorder are perceptible, especially where any buboes are open or discharging, for, according to him, all such pestilential ulcers are infectious for two months after the commencement of the attack.

In the urine too the bacilli are sometimes present, and in the faeces they may be found whenever haemorrhages take place from the intestines.

Moreover, needless to say, the organisms occur in the blood from whence they may find an exit when the blood is shed or when it is removed from the body by fleas or other biting insects.

III. Lurking places of the virus.

When the virus has once found its way out of the system of the last victim by one or other of the channels described above, the usual places where it hides or, as it were, lurks about, are:-

(1) dark unventilated houses.

(2) articles of clothing.

In the former the bacillus thrives, although it has not yet been satisfactorily determined whether infected houses mean merely rat-infested houses. This question will be further dealt with when we go on to consider the conditions which favour the persistence and spread of plague. For the present it may be mentioned that in some places in India, plague is said to have appeared again on the re-occupation of houses as many as forty days after their evacuation, The significance of a point of this nature in dealing with the subject of preventive measures to be adopted during an epidemic, is too evident to require any special mention.

With regard to clothing as a sheltering place for the plague germ, instances have been put on record to show that the infection has clung with tenacity to articles of this kind for three or four weeks. The importance of keeping such a possibility in mind, also from the point of view of prevention, is again perfectly manifest, and we shall take up its further consideration presently under the next heading.

IV. Modes of transport of the virus.

Suppose now that the virus has found a suitable hiding place after the exit from the body of its last victim, the next question calling for special notice at this stage is, how does it get transported, overseas and overland, from one locality to another?

From observations made and accounts given of numerous outbreaks of the disease, we are able to gather that:-

(1) The infection may be carried across the seas by,-

(a) Rats and possibly other animals.

(b) Convalescents.

(c) Infected clothing.

(d) Persons in the incubation stage of the malady, for short distances only.

The matter of rats being the carriers, and the most important carriers of the trouble to distant places beyond the seas, is now of course generally believed in, though it is still not credited by the followers of the Bruce Skinner school, as has already been pointed out along with the explanation given of the mode in which they believe the infection to be transported in ships. Their view is certainly a plausible one and it commends itself, at any rate, to further investigation. That rats have a peculiar fancy for the holds of ships and are the most common variety of stowaways, that they frequently board vessels at plague-infected ports without troubling to submit themselves to any form of medical inspection prior to embarkation, that they have a way of migrating from a locality especially when they find that members of their own community are dying there in unusual numbers, and that they are able to harbour the germs of the disease in their system, are all matters of common knowledge at the present day. But that they are, when infected, a source of danger to those on board during the voyage and to those at ports where they unceremoniously disembark without undergoing any period of quarantine, and, further, that they constitute a source of danger to man by reason of the presence of some suctirial insect that lives as a parasite on their blood and subsequently bites human beings in the neighbourhood, in accordance with the flea-hypothesis, are the very points which are not admitted by the set of observers who say that man derives the infection not from these rodents but from the same common source as they do. But as we have already stated before, and as we take the opportunity here to repeat, present opinion entirely incriminates the rat as a source, indeed as the most important source of infection for man. It is on this belief that some of our present methods of dealing with the prevention of spread of the disease are based, namely, by the destruction of rats on ships, on wharves, in warehouses and similar places. The description of the Clayton apparatus used for this purpose on ships, as well as for the general disinfection of the holds of vessels, will be given later on when dealing with the subject of the prevention of plague.

Convalescents, especially from the pneumonic form of the malady, may transport the infection for considerable distances, taking into account the rapid rate of movement of vessels in modern times, and having regard to the fact that the sputum of convalescents after pneumonic plague may contain the living germ of the disease for as many as thirty-three days after the return of the temperature to normal. The last circumstance is analogous to what has been noticed as occurring after cholera, namely, that the specific organism lives in the intestines for a long time and has indeed been found in the living condition there, as many as six weeks after the patient has been discharged from hospital as cured.

We now pass on to the subject of infected clothing as a means of transport for the virus to places beyond the seas. Such articles, as we have already seen, constitute one of the favourite lurking places for the virus outside the body, and so they may very easily act as a means of carrying the infection to distant parts. A knowledge of this fact guides us in taking certain precautions against the spread of the disease, namely, by placing restrictions against the carrying of soiled, and hence probably infected, linen on ships, and by causing soiled linen to be thoroughly disinfected before being landed at any port. The matter will be taken up again presently when we pass on to consider the modes of transport of the infection overland.

Persons in the incubation stage of the disease may well be the means of carrying the infection, but this they can do only for short distances, as the incubation stage of the disease is a short one. In the opinion of the Indian Plague Commissioners, the period of incubation in the case of plague is well within five days.

As a matter of fact, apart from theoretical possibilities, plague has hitherto shown little tendency to spread on boardship. Under the terms of the Venice Sanitary Convention of 1897, a "healthy ship" is any ship, even though coming from an infected port, which has had no death or case of plague on board, either before its departure, during the voyage or on arrival. Such vessel is entitled to free pratique, but the authorities at the port of arrival are at liberty to impose such restrictions as are laid down by the Convention. So far as the Indian epidemic is concerned, the medical inspection of outward bound vessels was commenced systematically at Bombay port in February,1897, and at Karachi,Madras and Calcutta shortly afterwaeds. The practice at first was that any persons with symptoms of plague were prevented from proceeding on the voyage, the inspection being made on board except in the case of pilgrim vessels. From the following year these inspections were carried out on shore prior to embarkation, in consonance with the principle formulated at the Venice Convention referred to, the object being to obviate the danger of the admission on boardship of persons suffering from evident signs of plague. It is of course impossible to detect cases in the early part of the incubation period by any method short of placing everyone in quarantine, prior to embarkation, for the full period of incubation. So far as the clothing went, at first only such portions of it as were considered to be contaminated, or even suspicious, were subjected to disinfection. The Indian Plague Commissioners in their report recommend more stringent measures, and accordingly it was ruled that the bedding and clothing of native crews and of all deck and third class passengers, as well as of native servants, should be disinfected on shore previous to the sailing of the vessel from Karachi, Bombay and Calcutta, for ports outside India. At Aden the practice has been to grant free pratique to all "healthy" vessels, even though the passage from an infected port occupied less than ten days, provided that the crew and passengers submit to medical inspection, that the soiled linen and personal effects of passengers appearing to be contaminated, are disinfected, and that the health of crew and passengers is watched for ten days from time of arrival, and the crew allowed to land only on duty. As the medical inspection and other restrictions placed on vessels involve delays, ships from infected ports using Aden as a port of call, generally prefer to remain in quarantine. With reference to the utility of these measures and to the little tendency for plague to spread on boardship, it may be noted that very few cases of the disease have been landed at Aden ever since the epidemic first broke out at Bombay in September, 1896.

(2) The infection may be carried overland by:-

(a) Healthy people merely conveying the poison on their person or clothing, without themselves taking the infection.

(b) Persons in the incubation stage of the disease.

(c) Infected clothing.

(d) The migration of rats.

Endless numbers of epidemics have from time to time been described to illustrate the routes selected by this disease and the steady march of the latter along the lines of land traffic, such as were so commonly in use in the East until a few years ago, and such as we have seen still exist in many parts of the north-west frontier of India, e.g. the high road to Khorassan and the neighbouring places. Many of these accounts are exceedingly well written and very interesting indeed, but they all go to show that the infection is transported in one or other of the ways we have indicated.

That healthy persons who have not taken the infection themselves, can still act as mechanical carriers of the virus on their person or clothing, has been well exemplified by means of a certain authentic case placed on record. At Glasgow two young women worked side by side in a factory. One of them had occasion to nurse a neighbour's child who had contracted plague; she did not take the infection herself, but the girl who worked by her side at the factory got plague and died of it, although she had had no direct communication with any other person suffering from the disease, and the only connection she had with the malady was the indirect one mentioned. The possibility suggests itself that the girl who had nursed the plague-stricken child carried on her person or clothing an infected insect, probably a flea, derived from that child, and that she unwittingly passed it on to her unfortunate neighbour at the factory.

Persons in the incubation stage of plague may, as we have seen before, transport the infection, but they can do so only for short distances. In the case of India, the spread by this means has been noticed to be slow, owing partly to the shortness of the incubation period of the disease, and partly to the measures generally adopted to prevent spread. The method that was the first to come into vogue, in October, 1896, consisted in the medical inspection of all passengers leaving Bombay city and other stations. On the 4th February, 1897, the Epidemic Diseases Act (iii of 1897) received the assent of the Governor General of India, and thereafter the system of medical inspection was improved as well as extended, suspected persons being at first detained in special camps, a plan which later on was abandoned. It was found, however, that the danger from persons incubating the disease was greater in the case of those journeying by road than in that of travellers by rail, but in no case was there a risk of the infection being carried far, owing in part to the incubation period being short and in part to the fact that travelling cannot be done nearly as rapidly by road as it can by rail. This point is well illustrated in the account given in the Plague Commission's Report of the epidemic which occurred in 1897, at Sholapur, a town in the Deccan, near the Hyderabad frontier. Although some 2,200 deaths took place at Sholapur within five months, and notwithstanding the fact that nearly one-half of the population fled in the early part of the outbreak and, despite the guards on the roads, found their way into Hyderabad territory, still the disease did not extend more than about sixty or seventy miles beyond the frontier.

We return again to the question of transport of the virus by means of infected clothing, a circumstance of which numerous instances have at various times been recorded. The danger of this is, of course, very considerable in India where the system generally prevails of "dhobies" washing soiled linen, frequently without previous boiling or other mode of disinfection, often in little ponds (called "tanks" in India) or in pools of water many of which are at the same time used by the neighbouring villagers for bathing, washing cooking utensils or for supplying water for drinking purposes. The danger of infection being carried to rather more distant places than within the limits of the same town is also considerable when clothing containing the specific virus is conveyed by railway or sent through the post. Against the latter contingency the postal authorities have adopted the precaution of issuing prohibitive regulations. Against the possibility of such infected articles being carried by rail, many regulations have from time to time been put in force and subsequently modified as considered necessary and proper. The views expressed by the Indian Plague Commissioners regarding the restriction of movements of travellers and their personal belongings by rail, are as follows,- (1) any system of land quarantine to detain passengers within infected areas, or from these into adjacent uninfected areas, has not been found in practice to prevent the spread of plague, (2) any system of medical examination on railways short of keeping travellers in detention for the ordinary incubation period, must be defective, (3) it is unnecessary to examine travellers medically between places in an uninfected area, and (4) disinfection of the personal effects of travellers by rail should not be attempted, partly because disinfection to be of any use should be thorough and this would entail delay and inconvenience which would not be justified by the results, and partly because people can evade disinfection of personal belongings by despatching these by goods trains and the disinfection of articles sent by such is an impossible task. With reference to this matter of clothing being a means of transport for the virus, in addition to being, as we have said, a lurking place for it, we might quote the experience of the village of Eyam, in Derbyshire, in 1666, the year following that in which, in the city of London, "Death on his pale horse, trampled on 3,000 victims in one ghastly night". The plague was carried thither in patterns of cloth sent from London to a tailor in the little village. Mead, in his work "On the plague" (Dublin, 1767, p.217) writing of this case, says "a servant who first opened the box, complaining that the goods were damp, was ordered to dry them at the fire but, in doing it, was seized with the plague and died. The same misfortune extended itself to all the rest of the family, except the tailor's wife who alone survived. From hence the distemper spread about and destroyed in that village and the rest of the parish, though a small one, between two and three hundred persons". Dr J.F.Payne, whose short but exhaustive article on plague we take this opportunity just to mention here as one that amply repays perusal, writes that "while the epidemic influence lasts, there is abundant influence that infected clothes, etc. are among the means by which the plague spreads". He goes on to quote the instance of two condemned criminals in Egypt who, in 1835, were for the sake of experiment placed in the clothes and beds of those who had died of plague; they both took the disease and one of them succumbed to it. On the other hand, there are cases on record in which infected clothing is said not to have conveyed the infection, although for our purposes this negative evidence is not of the same value. Thus, the same writer, referring to the Egyptian outbreak of the same year, 1835, mentions that "the hospital at Cairo, where 300 plague patients had been treated, was used, without ever changing the bed coverings, immediately after the epidemic, for other patients without harm". Another instance of the transport of the infection by means of cloth goods we shall see when we take up the study of the "Pali plague" later on.

As to the migration of rats by land acting so as to transport thr infection, nothing remains to be said in addition to what we have already mentioned, unless it be just to refer to the comparative ease with which these little animals are able to travel from one quarter of a town to another, or indeed much greater distances overland, including river routes. Regarding the latter we shall have a good deal to say by and by, when studying the origin of the special outbreak we propose to describe. We need not again allude to the Bruce Skinner theory of the probable harmlessness of such migratory acts on the part of these creatures even from infected areas. Suffice it to say, by way of repeating what we have already stated before more than once, that in the present state of general opinion such a circumstance is regarded as highly objectionable and looked upon as ominously full of danger to the inhabitants of the areas invaded.

V. Vehicles by which the virus is conveyed into the system.

Taking for granted that the virus has found its way into a fresh locality by one or other of the modes of transport mentioned, we naturally ask ourselves, by what vehicles is it conveyed into the system of a new victim? Such vehicles are:-

(1) Food (abdominal and septicaemic forms).

(2) Insects (bubonic form).

(3) Breathing air (pneumonic form).

(4) Soiled fingers (cervical form).

(5) Simple skin contact (bubonic form).

In this connection the subject of a water-supply for drinking purposes may be dismissed at once for, so far as is known, no relationship has yet been traced between either the incidence or the distribution of the disease on the one hand, and anything connected with a water-supply on the other, and so for the present, at any rate, plague finds no place on the list of water-borne diseases. We qualify our statement by saying for the present, since the possibility of drinking water eventually turning out to be a vehicle of convection for the virus of plague, as it undoubtedly is for those of cholera and of enteric fever, must be kept in mind. Some indeed, even at the present time, lay a certain amount of stress on this possible source of infection. In every outbreak of the disease the water-supply should no doubt be made the subject of careful investigation. An instance has been recorded in which a stagnant pool of filthy water was believed to have been concerned in fostering the plague-infection and the spread of the disease, in a village on the island of Bombay. Yet under ordinary conditions the bacillus appears to die out rapidly in water.

Food is undoubtedly a very common medium whereby the organism is conveyed into the system, even more so than was formerly believed to be the case. It is to Simpson, as well as to Hunter of Hong Kong, that the credit is due of being among the first to carry out a series of feeding experiments in a careful and scientific manner. Simpson demonstrated that in the case of rats, mice, monkeys and various other domestic animals, including poultry, plague was invariably communicated by the ingestion of infective material; and Manson points out that susceptibility to plague on the part of the animals of the farmyard, and the chronic and ill-defined nature which the disease in them frequently assumes, are probably "important factors in continuing the disease in the endemic centres where people, cattle, pigs and poultry are often housed under the same roof and even in the same room" as man. Referring to rats in particular, and to their infection viâ the mouth and alimentary system, Hunter writes that this "would appear to be the most frequent mode of dissemination of plague amongst rats". It has, however, been argued that inasmuch as experiments have shown that it requires a comparatively large dose of the virus to be taken in this way to produce a positive result, and considering that human beings are not often likely to be fed on large amounts of grossly contaminated matter, the method of infection by the gastro-intestinal tract may in their case be practically neglected. Still in spite of a certain degree of the contradictory element in the observations of different workers on this subject, it holds good that infection may be and, probably more often than is thought, is actually conveyed into the system along with food,- a fact to be kept in mind when framing our system of preventive measures against plague.

As regards insects being vehicles for the carriage of infection, much has been written and a great deal of discussion held, since the theory was first advocated by Dr P.L.Simond as the result of his studies in connection with the Indian epidemic up to August, 1898, and the flea was made responsible for acting as the carrier of the virus from infected rat to man. The point is full of the deepest interest and we shall go more fully into it presently when we take up the study of the channels of infection or ports by which the virus finds entrance into the body of man.

Meanwhile, passing on to the subject of breathing air, we find that there can be no doubt entertained as to this being responsible for conveying the poison into the system of the uninfected in a certain proportion of cases. In the pneumonic form of plague the nasal secretion thrown out in sneezing, or the sputum brought up in the act of coughing are very apt to contain the bacilli in large numbers, and the spray produced by the patient in the atmosphere around him is highly infectious for those in constant and close contact with him, especially under conditions of overcrowding and deficient ventilation. The infectivity of pneumonic plague is of high degree as compared with that of the bubonic form of the disease, and it was found by the Plague Commissioners that in the circumstances of good ventilation that obtained in authorised camps and in dry weather, this infectivity was much less than in overcrowded cities or unauthorised camps.

The fingers contaminated with plague-infected material, finding their way into the mouth, have been known to communicate the disease. The mode of convection by such a vehicle is generally associated with the cervical form of the disease and occurs most frequently in children.

That simple skin contact may be the means of convection of plague infection in the bubonic form of the trouble, is a matter over which there has been much debate, and we shall take it up presently under the next heading.

VI. Channels of infection or ports of entrance.

Granting that the virus has found its way to a fresh locality and has discovered a suitable vehicle to convey it into the system of an uninfected person, the question that next arises is, by what ports or channels does the poison effect an entry? Observation has shown that the following are the ways in which admittance into the body is most commonly gained by the plague virus:-

(1) Unabraded mucous membrane, such as the conjunctiva, nasal and buccal mucous membranes, and the lining of the alimentary tract.

(2) Submucous and subcutaneous tissues, through abrasions and insect-bites.

(3) Unbroken skin, aided by friction of clothes, etc.

As regards the occurrence of infection through unabraded mucous surfaces, not only is the possibility of this quite conceivable, but cases of it have from time to time been actually observed and recorded. Thus, for example, a patient suffering from pneumonic plague coughed up while the nurse was stooping over to attend to him, and discharged a germ-laden spray some of which reached her eye and imparted the disease to her, with effects that proved rapidly fatal to the woman. Again, when a child puts a finger contaminated with the specific virus, into its mouth, or a person ingests food similarly infected, or inhales into the respiratory passages a spray the particles of which carry the organism, infection occurs viâ the buccal, alimentary or respiratory mucous membrane, as the case may be.

Of course where abrasions are present, the entrance of the poison comes to be a comparatively simple matter, but in the case of the skin, at any rate, it has been noticed that the abrasion requires to be fairly recent. It is a common enough occurrence for cats to be infected by the blood of the rats on which they prey, viâ the little scratches made on their gums, tongue, tonsils, etc. by the spicules of bone of their contaminated victims.

Intact epidermis is regarded as being an insuperable barrier to the entrance of infective material and this explains the impunity with which so many autopsies have been performed and so many plague corpses handled. Much discussion has taken place in connection with the occurrence of infection resulting in the bubonic form of the affection, through the unbroken, unabraded skin. Some have held that minute abrasions, perhaps invisible to the naked eye, are invariably present in such instances, as for example in the case of the natives of India who, to a large extent, go about unshod. But against this opinion it has been argued that the wearing of boots or shoes and trousers does not afford protection in the case of Europeans in whom, although plague occurs much less frequently, the buboes have identically the same distribution as in the unshod natives, that is, about 66 per cent in the groin, 22 per cent in the axilla, and 12 per cent in the neck. If going about unshod and therefore having abrasions of the skin, be they ever so small and invisible, were factors of importance in the occurrence of infection viâ the skin, then inguinal buboes should be more common in the case of the native than in that of the better clad European. But such is not the case for, as we have just pointed out, the proportion according to hospital statistics is the same in all races and in all countries, that is, the relation of primary buboes in the cervical, axillary and inguinal regions respectively is roughly as 1 : 1.8 : 5.5- As Sir Thomas Fraser has very well shown, the relative distribution of the buboes is a great deal more closely related to the areas of skin draining into each of these three sets of glands, than it is to any differences of race, clothing or liability to injury of the skin surface. Thus, the frequency of inguinal buboes being three times that of axillary, and five and a half times that of cervical buboes, corresponds to the fact that the area of skin draining into the groin glands is three times as great as that draining into the glands of the armpit, and five and a half times as great as that draining into the glands of the neck. By way of explaining the frequency with which the glands of the groin are affected in bubonic plague, as compared with those of the axilla and of the neck, Hunter, of Hong Kong, says that just as in enteric fever the virus, no matter how introduced, localises itself in Peyer's patches, so it does in plague. In support of this view he further states that in feeding experiments he has succeeded in causing animals to be infected viâ their intestinal canal, by means of contaminated food, and has found them to develop inguinal buboes. Davidson believes that, in such instances, the fact of the matter is that the virus, absorbed from the intestinal tract, affects first the abdominal lymphatic glands and, as it were, by a secondary extension, the glands in the groin become affected. The question now comes to be that if the intact epidermis constitutes an insurmountable barrier to the virus gaining an entrance through the skin surface, if the theory regarding the constant presence of abrasions on the skin is not to be accepted, and if the suggestion made by Hunter is not satisfactory, then how are we to explain the clinically observed fact that the groin glands are much more commonly affected in bubonic plague than are those of the axillary and cervical sets? This is where the "flea hypothesis" steps in and offers a very ready explanation indeed. When Simond first suggested the idea that to the agency of some suctorial insect was probably attributable the spread of the infection from rat to man and from sick to sound, he did so after consideration of the epidemiological and experimental aspects of the subject. His argument is that there is little doubt of the great influence of rats in the spread of plague, that in this influence is found an explanation of the various irregularities met with in plague epidemics, and that, inasmuch as the mechanism of the propagation of the disease involves the transport of the virus by rat and by man, this transmission from rat to rat, man to man, or one to the other, is due to the agency of some parasite, and that therefore any preventive method to be complete must be directed against all three factors, namely, rat, man and parasite. Going further into the subject, he says that the interval between the introduction of the disease into a fresh locality by man, and its subsequent appearance there in epidemic form, corresponds to the time required for the disease to develop among the rats. He does not, however, at this stage adduce sufficient proof in support of his views and these are therefore severely criticised in the Report of the Plague Commission. Referring to two maps of the Bombay Presidency given in his paper to show for each place the time of first imported and first indigenous case, the Commissioners say that the "dates in Simond's maps to establish that a prolonged period intervenes between the importation of infection which originates an epidemic and the resulting epidemic are, considered as evidence of the truth of that theory, entirely fallacious". Nor does the Commission look with favour upon his view that a parasite, the flea, is the chief agent in the convection of the virus of plague, under natural conditions, for they regard his experiments as very incomplete, yet in the light of our present knowledge we cannot reject the idea that some insect of a suctorial kind may, as observed by Yersin and others of the French school, be responsible to a certain extent and under certain conditions, for the spread of this disease. The heavy incidence of plague among the Jains, a caste of people in India, whose religious motto expressed in Sanskrit is "অহিংসা পরমো ধর্ম " (Ahinsha paramo dharmo, lit. "Not to kill is the greatest virtue") and who therefore refuse to destroy any form of animal life, has frequently been cited in support of this view. It is at least certain that the flea does remove the bacillus with the blood which it sucks, and the evidence of reliable experimentalists is to the effect that they have been able to impart the disease to animals through the bite of such infected insects. Indeed, according to Hankin, the plague bacilli appear to multiply in the stomach of the flea. So far as the mechanism of the process of inoculation by such an insect goes, it is said that when the flea proceeds to bite, it first empties, or injects the contents of its stomach into the person on whose skin it alights, before commencing to suck the blood, and that the germ of plague contained within it, is thus inoculated into the person bitten. It used formerly to be said that the rat-flea did not attack man, and Hunter relates how he tried in vain to make one bite him; as the reason for his failure it has been suggested by some that probably the experiment was attempted in the daytime, while the habits of the insect are nocturnal. At the present time no weight is attached to the statement regarding the rat-flea not attacking man, for it has been found that many varieties of this insect live on the rat, and that at any rate some of them are ready enough to bite man if they get nothing they like better. Indeed, Tidswell has identified some three different species on rats, that are known to bite man. Fleas are parasitic creatures, and, therefore, when a rat dies and its body cools down, they leave their dead host and are quite open to attack a human being. Careful observations on this subject have been made by Ashburton Thompson in connection with the cases among Europeans in two at least of the Sydney epidemics. In every instance the plague was found to have been contracted in storehouses infested with rats, the patients being employees who worked in these stores by day and slept at nights in the plague-free suburbs of the town. So it was evident that infection must, in each instance, have been acquired during the day at the storehouses.

Further, in every case dead rats were discovered about the premises, and there could be no doubt of these animals having died of plague as the specific bacilli were found and demonstrated in their bodies. The point then came to be, how did the organisms find their way from rat to man? It was shown that in no case was the infection contracted directly by the handling of these rats, either living or dead. Moreover, each patient was carefully examined and no abrasions were found on the skin of any of them to account for the entrance of the virus. All the patients were shod and clad, so that the bacilli, presuming them to have been scattered about the stores, could not have come in direct contact with the skin surface, even allowing for the presence of minute, invisible abrasions. It is manifest that some indirect agency must have been at work in carrying out this deadly purpose. The Indian Plague Commissioners do not throw the responsibility on the flea, for their view is that Indian experience attaches no importance to such agency in the spread of plague infection. Taking into consideration the entire subject of man, rat and flea in connection with the spread of plague, we might sum up the facts in the following manner,- (1) from the evidence that has accumulated chiefly from a study of the Sydney epidemics, there appears at the present time to be very little doubt that man derives the infection most frequently, though not exclusively, from rats, and (2) the points in favour of the mode of transmission by the agency of suctorial insects are very strong indeed. Regarding the flea hypothesis, it must be said that, prima facie, the proposition appears a little difficult to credit in some ways, for, if correct, plague comes to occupy a position so far unique amongst bacterial diseases in that insect-transmission has never yet been demonstrated in any of them as it has in protozoal diseases, both in man, e.g. malaria, trypanosomiasis (trypanosome fever, sleeping sickness, relapsing fever, Leishman-Donovan or Dum-dum or Cachexial fever and Kala-azar), and in animals, e.g. piroplasmosis, trypanosomiasis (surra, nagana). The idea was suggested by Zammit, of Malta, in the case of a bacterial disease like Malta or Mediterranean fever due to infection with the micrococcus melitensis, for that observer sought to make the mosquito responsible for being a carrier of the germ in this disease. The suggestion has, however, been negatived by the experiments made by Horrocks, the results being published in 1905. Yet, when we consider, on the one hand, the complete manner in which the theory, in the case of plague, explains away many of the facts connected with the transmission of the virus and the spread of the disease to man, and when we take into account, on the other hand, the observations made during the Sydney epidemics, coupled with the results of research on the subject, carried out by reliable workers, in the way of biting experiments made with fleas on monkeys, as well as injection experiments on guinea-pigs with a trituration of infected flies in bouillon (Yersin), the least we can do is to repeat that the arguments in favour of the hypothesis regarding the flea are very strong in reality. Indeed, they seem to outweigh the fact that, owing to a deficiency in our scientific methods, we have not as yet succeeded in demonstrating insect-transmission in bacterial diseases, a circumstance against the possibility of the occurrence of which there is no evidence whatsoever and one which may perhaps be entirely attributable to a want of sufficient skill or of proper methods of investigation. There is not a very great deal known about either fleas generally or rat-fleas in particular, considering the important position these little creatures have come to attain from the discovery of the part they play in the spread of plague and the amount we ought therefore to know regarding them from all points of view. Writers from the plains of the Punjab, referring to this subject, inform us that they have observed a remarkable similarity between the "variations in flea prevalence and the variations in plague intensity". Thus, the appearance of fleas in increasing numbers in spring and again in autumn, and the fact that they practically disappear in summer and in winter, in the Punjab, correspond exactly with the period of greatest activity in plague incidence in the spring months, next in the autumn season, with a corresponding lull in summer and in winter. Hankin remarked in a similar way that in Agra a small plague epidemic came to a sudden end at the commencement of the summer when it was noticed that the fleas began to disappear.

Fleas belong to the family of Pulicidae, of the order Aphaniptera, and comprise a great many species. In India there are said to be three species which, as compared with others, are more frequently associated with man and certain domestic animals, as well as the rat. The Pulex serraticeps (vel felis) or the cat-flea, the Pulex irritans or the human flea, and the Pulex cheopis or the species commonly found on the Mus rattus, are the three kinds in question. The last is also sometimes, though not so often as the Ceratophyllus fasciatus, found on the Mus decumanus. They are all more or less nocturnal in habits, especially the Pulex cheopis, and although each variety has its own definite host, yet there is no doubt that it will attack man whenever it is driven by hunger or the absence of its host so to do. The experiments made by Captain Liston I.M.S. in this connection are very valuable indeed, and we draw attention to his interesting paper on "Plague, Rats and Fleas" read before the Bombay Natural History Society, on November 24th, 1904. While on the subject we might mention certain points of indirect evidence against the flea, further incriminating this little creature. Thus, the phlyctenules of plague cases often occur on the very parts of the body which are most liable to be bitten by fleas; the barefooted Indian and the well-shod Australian suffer to the same extent from inguinal buboes; the disease is found chiefly in places that are dark, ill ventilated, overcrowded, dirty and vermin-infested; clothing containing plague-infected rat-fleas has been associated with outbreaks; visits paid at nights to plague-stricken patients are a great deal more dangerous than visits by day, as the experience of ages has gone to show.

As we have already stated, minute skin abrasions are quite sufficient for infection viá the skin and for the occurrence of the bubonic form of plague, but such abrasions must be recent. After the lapse of 24 hours or less from the time of infliction of a small abrasion, the surface gets sufficiently glazed over to prevent infection from taking place on the simple application of the virus. Some workers on the subject have made experiments on the rabbit and have asserted that inoculation can be effected through the unbroken skin, but A. Thompson, of Sydney, has explained that in such instances, owing to the skin having been shaved immediately before the application, the chafed epidermis has allowed of the entrance of the poison, for if there is any delay in smearing the part with the infective material after the process of shaving, infection does not readily take place. Again, others claim to have caused infection of animals by inunction of their intact skin with plague cultures. Be this as it may, there is no doubt that infection viâ the unbroken skin is by no means a common method, so far as plague goes, as shown by the impunity with which post-mortem examinations are constantly made. The suggestion made by Hunter by way of explaining the mode of infection in bubonic plague and the reason for the inguinal glands being those most frequently affected, does not commend itself to us, for it seems that although some groin glands may become infected in a secondary manner from the abdominal sets which have received the poison from the intestinal tract, yet his proposition generally is untenable. The transmission of the virus by the agency of some suctorial insect, although not yet proved beyond all doubt in the scientific sense, certainly does appear more reasonable to credit in the case of bubonic plague and seems to have nothing against it beyond the fact that such mode of transmission has so far not been demonstrated in connection with bacterial diseases.

VII. <u>Conditions favouring the persistence and the spread of plague.</u>

The next question, one of the greatest importance in the epidemiology of plague, relates to the conditions which favour the persistence and spread of the disease. These may be grouped together in the following manner:-

(1) Factors which favour the saprophytic growth

of the specific organism or its vitality outside the body, including,-

(i) Filthy condition of houses and surroundings.

(ii) Absence of sunlight and ventilation and the presence of overcrowding.

(iii)Other insanitary conditions generally, including imperfect burial of the dead.

(2) Presence of rodents and other susceptible animals about dwellings.

(3) Presence of insects which carry and inoculate the virus.

(4) Factors which increase the virulence of the plague bacillus, such as,-

(i) Passage of the organism through certain animals.

(ii) Special culture media.

(iii) Excess of $CO_2$

(5) Wars, pilgrimages, and social or political changes leading to movements of population.

(6) Climatic factors.

As regards the power which the plague bacillus has of living saprophytically, experience has shown that under certain conditions not yet thoroughly understood, this organism has the power of surviving outside the body for a considerable time, provided it is not exposed to the action of sunlight or to the drying effects of exposure to the air. Thus, in cloths, skins, various textile fabrics and similar materials, the organism may live and retain its infectivity for a long period, as was illustrated in the case of the outbreak in the village of Eyam, in Derbyshire, in 1666, and numerous other instances more recent. That the germ can exist in this manner in filth accumulations in and around houses, such as are met with so frequently in Oriental cities and occasionally too in cities on the continent of Europe, is beyond all doubt. Hirsch lays the greatest stress on this aspect of the question and says "there is no point in the etiology of plague about which observers in all times and in every place have been so entirely in agreement, as that the origin and diffusion of the disease are closely associated with the injurious influences of a defective hygiene, and particularly with domestic misery. Almost all the authorities on epidemics of plague in Europe during past centuries point to the accumulation of filth in the houses and in the streets, to defective disposal of faecal matter and other animal excreta, to overcrowding and insufficient ventilation of dwellings, and the like, as a real means of fostering the pestilence". We have already noticed the constant relationship which the housing of cattle and poultry in the close vicinity of human abodes, with the consequent deposits of filth, bears to the endemic occurrence of plague. These conditions decidedly favour the existence and growth of the bacillus outside the body, and thereby encourage the persistence and spread of the disease. It has been noticed that the reeds and rushes that so frequently cover the floors of native huts in India, and which used to be spread over the floors of old-time English houses, favour the presence of rats, while the cowdung floors of native houses in India, by affording a medium alkaline in reaction, encourage the extra-corporeal growth of the plague bacillus. Yet it is difficult to recover this organism from such cowdung floors. This raises the important question of place-infection. Suppose the discharges of a plague patient are allowed to contaminate the floor of a house, it is probable that the place will retain the infection for a time, but sooner or later the saprophytic organisms present will exert their antagonistic influence and destroy the germs of plague. In fact Kitasato, Hankin, Leumann, Liston and others have frequently looked for the plague bacillus in the soil of infected huts but have never been able to discover it, except where contamination has occurred with recent plague sputum. It would appear that plague bacilli probably exist in the soil for a time at any rate, but that, owing to deficient methods, we are unable to prove this statement by demonstrating the organism recovered from this source. Lieut-Col. Bannerman I.M.S., Director of the Plague Research Laboratory, Bombay, tells us that "recent experiments with artificially infected floor-soil seem to show that plague bacilli rapidly perish in the presence of saprophytic organisms and have completely disappeared after four days". The President of the late Indian Plague Commission, in a memorandum on the effect of insanitary conditions on the extension and virulence of plague in India, remarks that there is indirect evidence but no direct bacteriological proof that the plague bacillus can continue to exist for long periods of time in filth. Bacteriological methods have not as yet developed so far as to furnish us with a satisfactory means of detecting the plague bacillus in the soil of floors by separating them from the purely saprophytic organisms present there.

The absence of sunlight and of fresh air, as a factor favouring the persistence and spread of plague, is, and has for a long time been, universally recognised. Kitasato has shown that the plague bacillus perishes in four days when dried on cover-glasses and protected from sunlight, but that it dies in three to four hours when exposed to sunlight. It has been found that the heat of the tropical sun is sufficient to destroy the germ in a few hours, if it is freely exposed to its action. The Plague Commission's Report says that the disease is most frequent in dark, ill-ventilated and overcrowded houses, and hospital experience has shown that even the close contact of relatives and attendants, with plague patients, if the apartment is well ventilated, does not tend so much to spread the disease. The President of the Commission, moreover, in his memorandum referred to above, states as his opinion that the vitality of the organism is diminished and even destroyed by exposure to light and air. Needless to add how invaluable is a knowledge of these matters to anyone who happens to be responsible for the public health of a locality where the fell disease makes its appearance and who wishes to cope with its tendency to spread, with a reasonable hope of success. Intimately associated with the absence of sunlight and ventilation, is the presence, among other insanitary conditions, of overcrowding. In all large cities of the East a very considerable proportion of the people are so poor that they cannot afford to pay the rent of anything like a really sanitary building, with the result that they are compelled to live in dark, small, low-roofed places constructed on the most undesirable sites, low-lying and unwholesome; in addition, so as to reduce the cost of occupying such a dwelling-place, it is a common practice for a dozen or more people to cook, eat and sleep in a space that is barely sufficient to accommodate four persons. Concerning this point the remarks of the Plague Commissioners are very explicit, for, in their opinion, the factor most particularly concerned in determining the introduction and spread of plague in a house is the overcrowding of that house. We may put it thus, that of no disease is it truer and of none probably so true that overcrowding, imperfect ventilation and want of sunlight, with the accompanying filthiness of atmosphere and habitation, are the predisposing causes. Moreover, overcrowding implies the greater possibility of contact. These conditions are all correlated and it is a matter of impossibility to differentiate between their effects. Want, in some cases an accompaniment of the disease, may be present to lower the vitality and increase the susceptibility of the individual to the poison, but the other conditions mentioned are by far the more conducive to the development, persistence and spread of the trouble. On this subject the President of the recent Plague Commission expresses his views by saying that the extension of the disease and its great fatality are largely dependent on the vitiation of air in dwellings; that the cause of this vitiation is not only uncleanliness but the absence or insufficiency of means of ventilation and the presence of overcrowding which last operates chiefly by adding to air-pollution; and, finally, that an increase of moisture, temperature and $CO_2$, with a decrease of oxygen in the atmosphere, plus a want of sunlight, stimulates the growth and increases the virulence of the plague bacillus present, while these conditions together predispose the occupants to attack.

The other insanitary conditions that usually prevail in localities where the persistence and spread of plague are most marked, including imperfect burial of the dead, may well be considered along with two other circumstances, namely, the presence of rodents and other susceptible animals about dwellings, and the presence of insects which serve to carry and inoculate the virus. Discussing insanitation along with the presence of rodents about dwellings, the President of the Plague Commission says that plague may be regarded as an infectious disease fostered by insanitary conditions, especially air-pollution within dwellings, and by rats; that if both are present, the suppression of an extensive epidemic becomes impossible short of completely evacuating every infected place; but that, if there is no large number of rats present, the task becomes less difficult; whereas, if there is no great air-pollution within dwellings, the undertaking is not particularly difficult, as the most important agency in enhancing the activity and virulence being absent, the rat infection would soon cease to be an important factor in spreading the disease. With regard to the imperfect burial of the dead, though it is a circumstance that has been noticed from very ancient times in this connection, and is one that is known to be almost invariably associated with endemic centres of plague, we are still unaware of the exact manner in which it is concerned in favouring the persistence and spread of the evil. The matter of the presence of insects which carry and inoculate the virus, is one of the utmost importance, if the hypothesis is accepted regarding these creatures actually subserving such a function. It is unnecessary to say much more on this subject, except perhaps to point out that the thatched roofs and the grass or bamboo-mat covered floors of Indian abodes foster both rats and such insects as fleas and bugs, that the rope bedsteads (called "charpoys") used by the poorer classes, afford a happy hunting-ground for many varieties of vermin, and that these conditions, as well as the housing of cattle along with man, and every possible manner of insanitary condition, have been associated together in causing the persistence and spread of plague in India for years.

Proceeding next to consider the factors which increase the virulence of the specific germ, we find that passage through certain animals comes first. It is well known that both by artificial means and in a natural manner the virulence of the plague bacillus is susceptible of modification. Thus, the artificial passage of the virus by successive inoculations through a series of guinea-pigs, intensifies its potency. As an instance of the naturally occurring change in virulence sometimes observed in this organism, may be mentioned the gradual decline in case-mortality noticed in some outbreaks, and the fact that with the progress of such epidemics the cases become less frequently and rapidly fatal, showing a natural decline in the potency of the germ. We have already given a short account of the work done by Klein in connection with differentiating between two types of the plague bacillus, but we would now call particular attention to what he said regarding the manner in which he has succeeded in modifying the more virulent "human" type into the less virulent "rat" type of bacillus, by passage through rats previously protected by subcutaneous inoculation with Haffkine's prophylactic,-a case of the attenuation of a virus by passage through the system of animals.

Then there is the effect of special culture media and methods of cultivation. Thus, Yersin has shown that when the plague organism is made to grow on gelatine peptone media, the growth may be as virulent as the virus taken directly from a bubo. Moreover, he has demonstrated that the more rapidly growing colonies are less virulent or in other words, that rapid growth of culture diminishes the virulence of the germ.

As to the action of $CO_2$, we have already said that the presence of this in excess stimulates the growth and increases the potency of the plague bacillus, as was demonstrated by Dr Marsh in the laboratory at Bombay. This fact has been put forward to explain how it is that a few cases of pneumonic plague occur every now and again in the course of an epidemic of the bubonic variety of the disease, for the germ, coming in contact with a non-resistant lung, that is, one bearing a patch of pneumonia or of congestion and therefore having carbonic oxide gas ($CO_2$) present in excess, finds a suitable nidus to grow with increased virulence and so sets up the pneumonic form of plague. The presence of this gas in increased amount in the atmospheric air, associated with overcrowding and deficient ventilation, was remarked on by the Plague Commissioners in the manner we have already noticed. In this connection it is interesting to observe the relationship of plague-incidence to the presence of $CO_2$ in the ground-air (the"grundluft" of the Germans). A series of experiments were made in the Plague Research Laboratory at Bombay, in 1900, with the air aspirated up through tubes sunk to a depth of 3 feet in the soil, empty dwellings and their surroundings, in the most insanitary localities of the city, being selected for the purpose. The results showed that the $CO_2$ in the ground-air was not excessive under the rooms with cow-dung floors as compared with other rooms, and moreover, that its amount increased with the rainfall. Now, it is well known that the ground-air may, under certain conditions, pass from soil into atmosphere, especially when the temperature of the atmosphere is lower than that of the soil at a depth of say 5 or 6 feet. The colder atmospheric air, being heavier, presses on the ground-air and forces it out into the atmosphere wherever the resistance to such escape is least. In India it is the uncemented, mud floors of the native houses that best allow of this process going on, particularly during the cold weather nights when the difference between inside and outside temperatures is greatest, the air within the houses being warmest and lightest, and that outside being most cold and heavy. These conditions of season and temperature, which act so far by favouring the escape of ground-air into the atmosphere, correspond entirely with the observed seasons of maximum plague incidence in Bombay. For, it is during the very months of the cold season that the soil temperature at a depth of 5 feet being 85°F. and the atmospheric temperature being as low as 75°F. or even 65°F., there takes place, on the one hand, the escape into houses of the impure air shown by experimental observations to be contained in the soil immediately around and, on the other hand, the greatest incidence of plague. It was the celebrated German scientist, Pettenkofer, who first pointed out that the best measure of the biological activity of a soil and therefore of soil-pollution, was the amount of $CO_2$ contained in its ground-air. Regarding this, reference may be made to the results of the experimental work of Lewis and Cunningham, at Calcutta,- ( "The soil in relation to disease", 1875 ),- on the relation of the ground-air to the maximum cholera prevalence there in April, and again in November. They demonstrated that when cholera was at its height, the $CO_2$ in the ground-air at depths of 3 feet and 6 feet was invariably at its minimum, and further that the increase of $CO_2$ in the ground-air, being the result of interference with the escape from soil into atmosphere, rather than of greater production of that gas, the greatest cholera incidence usually occurred whenever most ground-air escaped into the atmosphere. The whole subject is one not only of the deepest scientific interest but also of the greatest practical importance in guiding the epidemiologist in the matter of prevention of such diseases as he is concerned with, by providing for proper house ventilation and doing away with overcrowding, soil-pollution, the excessive formation of $CO_2$ and its escape into the atmosphere of dwellings.

Next we come to the question of the influence exerted by wars, pilgrimages and other social and political changes resulting in movements of large masses of people, on the persistence and spread of plague. That all these can be factors highly instrumental in fostering the disease and scattering its germs far and wide, is undoubted, for while they imply a suitable medium for transport, namely man, healthy or, it may be, incubating the disease, they at the same time mean the inevitable presence of every possible insanitary condition, such as filth, overcrowding, proximity of sick and sound, an atmosphere saturated with the emanations of the sick, a lowered tone of general health, saturation of soil and surrounding media with animal refuse fitting them admirably as a nidus for the growth of the germ, abundance of body vermin and possibly of rats and mice, carelessness about personal cleanliness, about wounds of hands and feet, about clothing, food, dishes and water. To these may be added the devitalising effects of fatigue, privation and exposure such as occur in times of war, and the frequent imperfect burial of the dead necessitated under such circumstances. Not much requires to be said in support of the statement that such conditions may prove to be most important factors in the dissemination of the disease and, if proof be needed, it is abundantly to be found in the history recorded of many epidemics, both ancient and modern, even a mere summary of which would take up too much space to recount and would be but of historic interest. With reference to a spread being effected in this manner by the agency of human creatures, experience has taught us who have had in our hands the practical management of such troubles that, when an outbreak commences among a large number of people, it is a very wise precaution indeed not to act with haste in making public a report of the first cases, lest panic drive the people away from the infected centre and precipitate the very calamity that it should be the object to avoid, namely, the scattering of the trouble broadcast in all directions.

The climatic factors concerned in causing the disease to persist and to spread, will be considered a little later on.

VIII. Conditions affecting susceptibility to plague.

Now allowing that some or other of the circumstances are present to foster and to scatter the disease, we apply ourselves to the study of the factors which tend to make individual members of a community more prone than others to contract the infection. The most important of these are:-

(1) Age. (4) Habits of life.

(2) Sex. (5) Race.

(3) Occupation. (6) Food.

Age apparently exerts a marked influence over the incidence of plague, and, according to the report of the Plague Commission, the maximum incidence is between the ages of ten and twenty years, the next greatest between thirty and forty years, and the smallest from the time of birth to five years of age. The following table shows the age-periods at which the disease occurs, in order of frequency from greatest to least.

The incidence of plague per 1000 living is:-

| | | | |
|---|---|---|---|
| 42.5 | at age-period | 10 to 20 | years. |
| 41.6 | " | 30 to 40 | " |
| 36.25 | " | 40 to 50 | " |
| 34.6 | " | 20 to 30 | " |
| 31.6 | " | 50 to 60 | " |
| 22.3 | " | 5 to 10 | " |
| 19.37 | " | 60 - | - |
| 5.15 | " | 0 to 5 | " |

Thus, while no age is exempt, the highest incidence is broadly between 10 and 40 years of age, or, it may even be said, between 15 and 35 years. (Vide Appendix, Table III).

Sex in itself seems to exert no special influence over the susceptibility to or incidence of plague. It has been said that possibly women are relatively more frequently attacked than men, especially in Eastern countries where they spend a great deal of time in-doors in tainted dwellings. In the epidemic which we shall describe later, it will be seen that not only were women attacked to men attacked as 1.5 : 1, but that the women who suffered from plague were 5.7 per 1000 women living in the affected area, while the men who so suffered were 4.3 per 1000 men living in the same area, and, again, the case-mortality amongst females was 79.5 per cent, while that amongst males was 63.6 per cent. (Vide Appendix, Tables V, VI, and XII). The reports of the Parel and Grant Road Hospitals, at Bombay, on this subject, say that "approximately in relation to sexes, males have been attacked in rather more than twice the number of females, this being probably due to their greater exposure and partly to the fact that a large number of women and children left the city during the course of the epidemic".

Occupation, per se, has a doubtful bearing on this question of susceptibility though, in its relation to habits of life and to surroundings, it comes to be a matter of some importance. Thus, in the accounts of many epidemics of former times, it is related that tanners, curriers, hospital servants and others engaged in unwholesome forms of occupation, have shown a remarkable exemption. Even in the Bombay epidemic of late years it has been observed that the scavengers furnished very few deaths, and also that people engaged in manufacturing, carrying and selling oil, escaped to a considerable extent. In explanation of this last mentioned fact, it has been suggested that, inasmuch as the skin of such people is usually smeared with oil, the flea does not care to insert its proboscis through a layer of grease and so it avoids biting and inoculating them with the virus of the disease. It used formerly to be said that plague had a way of picking out the best and most respectable members of society and of sparing the least worthy, but this is one of the many statements that have from time to time been made with regard to this disease, without any foundation, as experience has shown us, and the belief in which has long since been abandoned. Thus, it used in days gone by to be said that plague was a disease of the Eastern hemisphere and that it was limited to the northern half of it, as it could not pass the equator, but recent outbreaks in parts of the West as well as in latitudes south of the equator, such as Australia and South Africa, have dispelled all ideas of this kind. Indeed such limitation to particular quarters of the earth's surface has never been demonstrated in the case of any bacterial disease as it has in that of protozoal infections where the distribution of each malady strictly corresponds with that of its particular carrier. Again, as lately as two years ago, when plague raged so badly in the Punjab, it used to be said on the north-west frontier of India, that the stations there were quite safe inasmuch as the Indus constituted an insurpassable barrier to the advance of the disease. This was soon disproved by the occurrence of plague at Dera Ghazi Khan city, about ten miles west of the Indus, late in December, 1904, and it was to hold charge as Medical Officer of Health of the cantonment of that name, adjoining the city, that we proceeded there early in January, 1905, and adopted such preventive measures as fortunately secured the freedom of the cantonment from the dread disease while it raged beyond the boundary pillars, in the city. But returning to our subject proper, we repeat that plague has by no means any special predilection for the most worthy members of society. Such a mode of selection is, moreover, not supported by the fact that our own profession has enjoyed such a remarkable degree of immunity. With regard to the special incidence of the disease among the clergy, we have already stated the opinion of the famous epidemiologist, Creighton, and we would here add that a similar liability on the part of those engaged in that calling was observed in the last outbreak in France, which occurred at Marseilles, in 1720, and spread thence through Provence. Of course it need hardly be added that whenever occupation is of such a nature as to lead to special exposure to the virus, or imply such faulty habits of life as tend to lower the general tone of the system, the proneness or susceptibility becomes corresponding in extent.

Race has little influence on susceptibility except again where it implies faulty habits of life, unwholesome occupation or insanitary surroundings. While no race enjoys an absolute immunity, those nationalities suffer least whose social and hygienic conditions are most favourable.Thus during the last outbreak in Hong Kong,the European community suffered least,the Japanese came next,then the Indians,while the Chinese residents suffered the heaviest plague incidence.In India too the superior social customs and hygienic surroundings of the Europeans generally,as compared with those of the natives,are fully in keeping with the very small incidence among the former in comparison with that among the latter. On this point Dr Bitter has made the very interesting remark that "La seule explication raisonnable que l'on pourrait donner pour l'immunité relative des Européens, c'est que par leurs habitudes de vie, ils sont mieux protegés contre l'infection".

Food, as a condition affecting susceptibility, is less important than the other factors we have considered, provided always that the food referred to is free from all contamination with the specific virus. It has been said that vegetarians are more susceptible than others but, apart from the possibility of a diet restricted more or less to vegetables allowing of the development of less vitality and power of resistance, the matter may be explained in other ways. Thus, frequently those who are vegetarians, in India at any rate, are so by reason of their poverty, and this in its turn implies faulty hygienic environment. In other cases, strict vegetarians, like the Jains of India, rigidly refuse to take animal life in any form and are therefore more liable to infection by the agency of vermin with which the members of this sect are always associated not too wisely but too well, an association which is very intimate, indeed often literally personal. No facts, so far as we are aware, have as yet been advanced to show that green vegetables are particularly liable to become contaminated with infective material in the fields and to convey the infection to man, as has been demonstrated to take place in the case of a protozoal disease like amoebic dysentery. The question of infection of grain and such foodstuffs is an important one in its practical bearings on the question of prevention.

IX. Causes of the secular extension of plague.

This subject involves points which unfortunately are, for the present, somewhat obscure in their nature.

One factor to which such extension has been ascribed is the increase which from time to time, and in the course of time, occurs in the virulence of the plague bacillus, owing to some causes at present unknown. The only reasonable suggestion that can be offered by way of an explanation of the phenomenon is that, as in bacterial diseases generally, so probably also in the case of plague, there occur cyclical fluctuations in the intensity of the virus. In addition, all extensive movements of population and other circumstances which facilitate the diffusion of the virus, and all conditions which tend to give the necessary predisposition to, or increase this in a people, such as poverty, defective hygiene, etc, naturally aid in the secular extension of the trouble. In connection with the long terms of quiescence or the protracted inter-epidemic periods which, as we have said before, characterise the epidemiology of plague, the question may well be raised as to what becomes of the germ of the disease during such intervals of respite? Is it annihilated in the locality for the time being, requiring a fresh introduction from some endemic centre for a new outbreak (as the followers of the "contagionist" section of the Ephodists hold in the case of cholera)? Or, does it in the meanwhile take on a saprophytic existence in the locality, requiring say passage through a suitable animal, for example the rat, or awaiting other favourable conditions, in order again to recover its parasitic nature and its potency for evil (as the members of the "localist" party of the Ephodists might say)? We are to a large extent still in ignorance regarding these matters and the causes which govern the rise and fall of epidemics at long intervals.

X. Causes of the seasonal exacerbations of plague.

We are somewhat better informed as to the manner in which an epidemic goes up and down in relation to the seasons of the year. The headings under which we may most conveniently consider this question are the following:-

(1) Climatic and meteorological conditions acting directly on the plague bacillus,

(a) By either promoting, attenuating or inhibiting its growth, through the influence of such conditions as temperature and either rainfall or drought.

(b) By causing a difference between air and soil temperatures at certain seasons, and favouring the escape of soil-air and hence the growth and virulence of the bacillus.

(2) Climatic and meteorological conditions acting indirectly by promoting ventilation and sleeping out of doors, and lessening overcrowding.

(3) Variations in the seasonal prevalence of the disease among rodents.

(4) Variations in the seasonal prevalence of fleas.

The first point in the discussion of this important matter comprises climatic and meteorological conditions acting directly on the plague bacillus itself in the way of either promoting or inhibiting its growth or attenuating it, the most prominent being atmospheric temperature on the one hand, and either rainfall or drought on the other. The lessons taught us by recent developments in the bacteriology of this disease help us to understand many a point in its epidemiology which would otherwise be quite obscure. Thus, taking into account the temperatures which, as stated before, were inimical or even fatal to the organism in artificial cultures, we are readily able to understand how it is that the disease is not peculiarly one of tropical climates and indeed why it should be that the typical conditions of such climates, namely intense heat, etc, do not favour it, and therefore why plague, during its present epidemic extension in India, has been observed to attain less formidable proportions in the hot plains of the Madras Presidency (exclusive of the high tablelands) than in regions further north; in short, it makes it clear why plague is really a disease of the subtropics. Moreover, bearing in mind that the organism does not flourish below 60°F (15°5 C) or above a temperature of 125°F (50°C), we are able to explain why, in a place like Bombay, the disease is in general a cold weather one, and why, when it used to occur in England, it usually selected the summer months. It must, however, be remembered that all these statements are only generally correct and hold good in the case of most epidemics and their seasonal exacerbations, and they therefore must not be taken, in a hard and fast sense, to apply to all outbreaks, for we have on record epidemics of plague which occurred, on the one hand, during a Russian winter, and on the other, during the tropical heat of a summer in Hong Kong. Again, generally speaking, the occurrence of rainfall has the effect of enhancing the incidence of plague by increasing, as we have seen, the amount of $CO_2$ in the ground-air, and also, if not excessive, of affording a suitable amount of moisture for the growth of the organism in external media. Drought, as a rule, tends to diminish the incidence of the disease by witholding this moisture, decreasing the $CO_2$ in the ground-air and allowing of the desiccation of the germ. In India, in the hot dry season before the rains, the surface soil becomes very dry and its temperature rises very high. The questions then naturally arise, does the organism, during the saprophytic life it leads in the soil, stay in the superficial or in the deep layers? If in the former, how does it resist the conditions of high temperature and want of moisture that prevail during the hot, dry weather? If it occupies the deeper layers, how does it pass from them to infect man? These are some of the problems in this connection that still await solution. Again, the plague bacillus accustomed to living under a special set of meteorological conditions, as for example those that characterise the cold season, appears to be unable to adapt itself to the alterations in external environment which accompany the onset of the hot and rainy seasons, for an outbreak occurring in the cold season dies out when the summer heat and the rains set in. It has also been said that inasmuch as a summer or rainy season outbreak declines with the advent of colder days, the plague bacillus associated with the former is able to adapt itself, though with a certain diminution in its power, to the circumstances that prevail during the latter season. With regard to these climatic conditions generally, the President of the Indian Plague Commission considers that they are not responsible for the occurrence and extension of the disease, as the temperatures found to be sufficient to kill artificial cultures of the plague bacillus in five or ten minutes, in laboratory experiments, are much below the heat given off by the sun's rays in many parts of India. Moreover, it is pointed out that the organism in such parts could hardly live long on the surface of the soil or just below, in open places exposed to the sunlight, as distinguished from the narrow lanes and courtyards of large cities, except if sheltered from the destructive action of the heat and light of the sun. This latter condition obtains within dwellings, where the heat and moisture favour the life and growth of the germ, unlike the too high or the too low temperature and the dry atmosphere outside.

We have already gone into the subject of the differences between air and soil temperatures at certain seasons of the year, favouring the escape of $CO_2$-laden ground-air into the atmosphere within dwellings, and we have considered the effects of this state of things in the way of stimulating the vitality of the organism, increasing its virulence and thereby acting as a cause of the seasonal exacerbations of plague.

Climatic and meteorological conditions may also exert a similar influence in an indirect manner. Thus, the fact that in the warm, summer weather many people, in tropical and subtropical latitudes and on the plains, sleep out of doors or, at any rate, keep the doors and windows of their sleeping apartments open at night, implies better ventilation and less overcrowding, as compared with what obtains in the cold season, and therefore less $CO_2$ and a less concentrated and virulent form of the poison (if present) in the atmosphere of the place, as well as less close contact between persons, sick and sound. Such conditions are in themselves very highly desirable from the point of view of both general hygiene and this particular disease, quite apart from the fact that on cold nights when people huddle together in stuffy and ill-ventilated rooms, there is a considerable difference between outside and inside temperatures, causing the maximum of soil-ventilation through the floors into the atmosphere of the dwellings.

In fact, sleeping in the open air at night means in itself the removal of the occupants for a portion at least of the twenty-four hours from the filthy surroundings that so frequently characterise the interior of households belonging to the poorer classes. This probably accounts to a considerable extent for freedom from the disease during the warm season of the year in a country like India.

Then, again, as a cause of the seasonal exacerbations of plague, may be mentioned the varying prevalence of the disease among rodents, according to season, but this merely raises the question as to what circumstances determine the seasonal fluctuations of the malady among rodents? This question is very intimately associated with that of the variations in the seasonal prevalence of fleas. We have already noted (vide p.145) what Hankin observed in connection with the disappearance of fleas at the commencement of the hot weather, and the sudden and simultaneous ending of an epidemic at Agra. We have also drawn attention to the evidence afforded by many workers on the plains of the Punjab, as to the manner in which variations in flea prevalence affect those in plague intensity. Lastly, we have mentioned what Tidswell, as quoted by Ashburton Thompson in his report on the second outbreak at Sydney, 1902, says as to having found many fleas on rats during the epidemic but few at the termination of it. The circumstance might help to explain the temporary cessation of an outbreak at a certain season, by reason of the disappearance, for the time being, of the disease carrier, but then this does not in any way make clear the cause of the seasonal recurrence. For, where does the flea, when seasonal conditions favour its re-appearance, derive the infection again? Is it from what Hunter in his report on the epizootic form of the disease, calls the chronic plague of rats and other animals? The results of Klein's most recent studies on the subject of the different types of plague bacilli and their relation to one another, have already been recounted (vide p.96-7). The whole matter still awaits much elucidation.

XI. Causes of the seasonal decrease of plague.

The usual history of an epidemic of plague is that, after increasing for a time varying with the amount of population and other conditions, it ceases to spread although the case-mortality continues high, frequently as much so as during the very height of the outbreak. Apart from the question of the disappearance of fleas from rats in the manner mentioned above, this decrease in the spread of the disease may be the result of (1) exhaustion of the susceptible, owing to several people leaving the locality, others falling early victims to the malady, and still others acquiring an immunity, to a greater or less extent, as the result of previous attacks or of repeatedly receiving small doses of the virus; (2) increasing resistance of the population to the virus, for the number of those we might call "insusceptibles" gradually increases both actually and relatively to the total remaining population; (3) some change probably occurring in the virus itself, owing to its passage through or culture on some outside medium, analogous to the manner in which, as we have seen, Hueppe says that the cholera organism, virulent when it leaves the body, loses its virulence in a large measure during its saprophytic stay in the soil. Davidson has remarked that the arrest of the spread of plague after a certain time is too definite to be ascribable to climatic conditions alone.

Having briefly discussed the various causes that are known to be (causally) associated with the seasonal exacerbations and the seasonal decrease of plague, we might appropriately mention at this place the seasons in relation to the disease as it occurs in some of its favourite haunts.

In its endemic centres plague may occur all the year round.

Epidemic seasons vary in different places, but they are nearly always the same in the same locality.

<u>India</u> has two epidemic seasons,

January to April = maximum.

June = minimum.

August to November = secondary maximum.

December = lesser minimum.

<u>Egypt</u> = Spring and early summer.

<u>Asia Minor</u> = Spring and summer.

Northern Europe = Generally late summer and autumn.

Places south of the equator have their epidemic seasons of plague at corresponding seasons of the year, thus Cape Town (S.Africa) and Sydney (Australia) have theirs from March to May.

XII. Causes determining the extinction of an epidemic.

We have just said that the manner in which, after a time, an outbreak ceases altogether to spread and, in place of doing this, dies down completely, is not ascribable to climatic conditions, or, at any rate, not to such alone. It would appear that the infective power and virulence diminish in the poison itself as the epidemic goes on. Thus, the case-mortality, though it varies in different outbreaks and at different periods of the same outbreak, is usually found to be lowest towards the end of an epidemic, provided of course care is taken to secure correct estimates by taking into account as many cases as possible, drawn from a large area and over a prolonged period of time. Then again, as a reason for the extinction of an outbreak, there is the fact that the number of susceptibles is constantly decreasing owing to one or other of the reasons enumerated above. The dying out of rodents, as well as every measure that tends to improve sanitation generally, will doubtless also give very material help in the stamping out of an epidemic. Taking the case of the great plague of London, we find that the reasons ascribed for the sudden and dramatic manner in which the scourge made its very desirable exit, in 1666, after having claimed no less than 70,000 victims in the preceding year, are many and various. It has been said that the great fire of London may be held accountable for the termination of that epidemic, inasmuch as it destroyed the numerous foci which the disease had established in the insanitary quarters of the city, but against this view may be cited the instances of other infected districts in England, as well as cases of several continental towns, where too the last appearance of the malady was marked as unusually severe and from whence the trouble vanished in as sudden and striking a manner without there having been any large fire to account for such disappearance. The phenomenon has been attributed to an exhaustion of susceptibles, but against this it has been argued that the explanation is not a sufficient one, for many people still open to infection returned to London on the first sign of decline in the epidemic. Then, again, it has been suggested that quarantine was the measure that caused the outbreak to die out, but as a matter of fact, quarantine was not in vogue at the time. Sanitary reforms have been given the credit of bringing about the termination of the epidemic in London, but again these were neither as instantly applied nor as thorough as would account for that happy result. The onset of the winter season has by some been accredited with putting an end to that outbreak, but the explanation is not accepted as a sufficient one and naturally the instances are quoted of the occurrence of plague epidemics even in the coldest Russian winters. Finally, there is the disappearance of the Mus rattus or black rat, the house or domestic species, from England and from Western Europe generally, which occurred contemporaneously with the vanishing of plague from all that region. The two circumstances have by many, in the light of advancing knowledge, been associated together in the relation of cause and effect.

The consensus of opinion at the present day is that while the disease may be acquired without the agency of rats, yet given no rats there can be no epidemic of plague.

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